Remarks

Claims 1-13 and 15-18 are pending. No claim has been amended or canceled.

Response to Claim Rejections – 35 USC § 103

To establish a *prima facie* case of obviousness, a number of criteria must be met. For example, all of the limitations of a rejected claim must be taught or suggested in the references relied upon by the Examiner; or they must be among the variations that would have been "obvious to try" to one of ordinary skill in the relevant art in light of the cited references. Moreover, one of ordinary skill in the relevant art must have a reasonable expectation of success in light of the combination of cited references. Importantly, the reasonable expectation of success must be found in the prior art, and may not be based on the Applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991); see MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

Regarding claims 1 and 15-18

Claims 1 and 15-18 stand rejected under 35 U.S.C. 103(a) as obvious over Perkins et al. (US 6,287,290).

Perkins does not teach each and every element of the claimed invention

The Examiner asserts that Perkins discloses "introducing [a] composition...to collapse the diseased alveolar (CLT) region." *Office Action* at page 2. However, the Applicant respectfully contends that the methods for lung volume reduction disclosed in Perkins do not target the alveolar region of the lung. Perkins teaches optionally sealing or occluding an air passage leading to the collapsed region of the lung by "delivering a plug..., typically at [*sic*] partially hydrated collagen hydrogel..." ***after*** the lung has been collapsed by vacuum aspiration or the application of external force. The plug is delivered to the lung bronchus and used to seal the air passage leading to the target lung segment. *See Perkins*, column 9, lines 24-29; column 10, lines 37-58; and Figure 4C.

Importantly, Perkins defines an "air passage" as a "segment of the branching bronchus which deliver[s] to and receive[s] air from the alveolar regions of the lung." *Perkins*, column 6, lines 34 -39. In light of the explicit definition of "air passage" in Perkins, a summary of human pulmonary anatomy is appropriate, in support of which the Applicant respectfully directs the

Examiner to Exhibit A (Figure 1-2) depicting a schematic diagram of the human airway. As shown in Exhibit A, the left and right bronchi are the two main tubes of the lung that extend from the trachea and branch off within the lung to form secondary and tertiary bronchi. The bronchi further branch to form smaller bronchioles and terminal bronchioles. At the ends of the terminal bronchioles are the alveoli. Based on the explicit definition of "air passage" in Perkins, the Applicant respectfully asserts that the methods of Perkins are limited to sealing the lung at the bronchi before the lung branches into its substructure.

In contrast, the Applicant's claimed methods relate to reducing lung volume in a patient by introducing material through a bronchoscope into a diseased alveolar region within the targeted region where the material induces collapse of the targeted region, promotes adhesion between one portion of the lung and another, and promotes fibrosis in or around the collapsed region of the lung. Thus, in stark contrast to the disclosure of Perkins, in the claimed methods the administered anti-surfactant-containing composition does not serve as a plug to ***occlude*** the air passage leading to the collapsed tissue region; rather, it acts to induce collapse, promote adhesion, and promote fibrosis. (*Specification* at page 1, lines 31 to page 2, lines 1-9.).

Furthermore, the "plug" to which Perkins refers is depicted in Figure 10 thereof. One of ordinary skill in the art would understand the term "plug" to refer to a non-flowable material, and the "plug" of Perkins is depicted as such in Perkins' Figures. Indeed, the provided example refers to a swellable collagen hydrogel that merely occludes an airway upon being positioned by a catheter. The positioned plug of Perkins does not promote collapse of the diseased alveolar tissue; whereas, rejected claim 1 is directed to the administration of an anti-surfactant-containing composition that promotes collapse of the diseased alveolar tissue.

Critically, Perkins does not explicitly or inherently disclose promoting stable volume reduction of a targeted region of a patient's lung by introducing a liquid material through a bronchoscope into a diseased alveolar region within the targeted region where the material induces collapse of the targeted region, promotes adhesion between one potion of the lung and another and promotes fibrosis in or around the collapsed region of the lung. Thus, Perkins does not expressly or inherently teach each and every element of Applicant's claims.

The claimed invention is not "obvious to try" in light of Perkins

The criteria for establishing a *prima facie* case of obviousness are outlined above. As explained above, Perkins does not teach every element of rejected claims 1 and 15-18. Further, the differences between the disclosure of Perkins and the rejected claims would not have been "obvious to try" to one of ordinary skill in the art because Perkins merely discloses the use of a plug delivered to the lung ***bronchus*** to occlude the "air passage" leading to the collapsed tissue region, wherein the region has previously been collapsed by the application of an external force or vacuum aspiration of the air contained in that region of the lung. In contrast, the Applicant's claimed methods relate to reducing lung volume in a patient by introducing a material through a bronchoscope into a diseased alveolar region within the targeted region, where the material induces collapse of the targeted region, promotes adhesion between one portion of the lung and another, and promotes fibrosis in or around the collapsed region of the lung. Importantly, the portion of the lung targeted in Applicant's claimed methods is the ***alveolar region*** (i.e., the region at the end of the terminal bronchioles), not the lung bronchus targeted by Perkins.

In other words, Perkins teaches a method in which a region of the lung is first collapsed, followed by occlusion of an "air passage." Moreover, the Applicant respectfully contends that the numerous and substantial distinctions between the claimed methods and the teachings of Perkins are beyond the scope of the variations that the Examiner may reasonably characterize as "obvious to try" to one of ordinary skill in the relevant art in light of Perkins. For example, the differences between the claimed methods and the teachings of Perkins cannot reasonably be described as merely selecting a particular species from a well-defined genus of limited scope. Nor can those same differences be reasonably characterized as the result of nothing more than routine experimentation or refinement of what was known in the art.

Perkins does not provide a reasonable expectation of success

Further, one of ordinary skill in the art would not have had a reasonable expectation of success in developing the claimed lung volume reduction methods in light of Perkins. Due to their understanding of "collateral ventilation", those of ordinary skill in the relevant art at the time the instant application was filed did not view the methods for lung volume reduction disclosed by Perkins as effective in producing atelectasis, and preventing the targeted region of the lung from receiving air flow. Collateral ventilation is the pulmonary phenomenon whereby apparently isolated alveolar regions are ventilated through passages or channels that bypass

standard airways. Due to collateral ventilation a section of a lung targeted for volume reduction via occlusion at the level of an "air passage" as defined in Perkins still receives airflow due to the presence of auxiliary airways, thereby preventing atelectasis.

Submitted herewith is Exhibit B, visually underscoring some of the pertinent structural and therapeutic distinctions between normal lung tissue and emphysematous lung tissue with collateral ventilation. Exhibit B consists of four illustrations: normal lung tissue; emphysematous lung tissue with collateral ventilation into which a bronchial plug has been inserted; emphysematous lung tissue with collateral ventilation into the alveolar regions of which a composition comprising a protease has been introduced; and the resulting reduction in volume of the emphysematous lung tissue after such protease treatment. Accordingly, the Applicant respectfully contends that one of ordinary skill in the art would not have had a reasonable expectation of success in developing the claimed methods of lung volume reduction in light of Perkins.

In further support of this analysis, Applicant includes herewith four references, marked as Exhibits C, D, E, and F, which discuss the highly problematic effects of collateral ventilation in bronchoscopic lung volume reduction therapy. The references disclose that collateral ventilation prevents atelectasis in bronchoscopic lung volume reduction when the lung is occluded in the bronchial portion of the airway (i.e., at the level of an "air passage" as defined in Perkins). In other words, the references establish that methods like those disclosed in Perkins are generally ineffective in achieving lung volume reduction. For the convenience of the Examiner, tabulated below are results from Exhibits E and F, outlining data collected 6-months post-treatment from a number of patients that received endobronchial valve therapy. Exhibits C and D are not disclosed in the table because Exhibit D provides no data and Exhibit C provides only short-term data from 4-weeks post-treatment. The endobronchial valve therapy discussed in Exhibits E and F entails delivering a device to occlude the airway in order to promote collapse and lung volume reduction. The long-term results establish that endobronchial valve therapy has little beneficial effect on lung function. For example, FEV_1, the most commonly used measure of lung function, improved (increased) minimally with the valve used in Exhibit E, and actually *declined* upon implantation of the valve from Exhibit F. Both Exhibits point to the detrimental effects of collateral ventilation, which render airway-based therapies largely ineffective.

Outcome Measure	Exhibit E, 6 months (n=179 pts)	Exhibit F, 6 months (n=45 pts)
FEV_1 (% Δ)	+5.3±28.2*	-4.7±19.1*
FVC (% Δ)	N/A	-3.9±23.4*
RV/TLC (% Δ)	N/A	N/A
6 MWD (Δ)	+4.3±31.6%*	+3.5±17.9%
SGRQ (Δ U)	-3.4±30.4*	-8.9±16.2

* Statistically significant compared to baseline

Furthermore, the purpose of the "tissue adhesives,;...occlusive balloons;...[and] self-expanding meshes, coils, and other occlusive structures" (column 2, lines 39-41) described in Perkins is merely to occlude an air passage. Given the dimensional and structural differences between an "air passage" and an alveoli, as described above, one of ordinary skill in the art would not have expected to be able to collapse an air passage upon deployment of these occlusive and sealing structures.

Consequently, the Applicant respectfully contends that one of ordinary skill in the art would not have had a reasonable expectation of success in utilizing the methods disclosed in Perkins for lung volume reduction. Moreover, the Applicants respectfully contend that the teachings of Perkins and the Exhibits provided herewith would have led one of ordinary skill in the art to conclude that it would be *unreasonable* to expect success in developing the claimed methods. Accordingly, the Applicants respectfully assert that no colorable argument can be made that one of ordinary skill in the art would have had a reasonable expectation of success in developing the claimed methods for lung volume reduction at the time the instant application was filed.

Based on the foregoing, Applicant respectfully requests withdrawal of the claim rejections under 35 U.S.C. § 103(a) based on Perkins.

Regarding claim 13

Claim 13 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins in view of Edwardson et al. (US 5,739,288). Claim 13 depends upon claim 1, adding the

additional limitation that "the anti-surfactant composition further comprises an antibiotic." The Applicants confess that they are unable to understand how Edwardson might be relevant to that claim limitation -- perhaps the Examiner intended to reject another claim or claims based on Perkins in view of Edwardson. Based on this possibility, below the Applicants explain why they believe that the combination of Perkins and Edwardson is not relevant to the patentability of any of the pending claims.

The Applicant asserts that the skilled artisan would not arrive at the claimed invention based on the combination of Perkins and Edwardson because the cited combination does not disclose or render "obvious to try" all of the limitations of the rejected claims.

As discussed above, Perkins teaches optionally sealing or occluding an air passage leading to the collapsed region of the lung by "delivering a plug…, typically at [*sic*] partially hydrated collagen hydrogel…" ***after*** the lung has been collapsed by vacuum aspiration or the application of external force. The plug is delivered to the lung bronchus and used to seal the air passage leading to the target lung segment. *See Perkins*, column 9, lines 24-29; column 10, lines 37-58; and Figure 4C. Importantly, Perkins defines an "air passage" as a "segment of the branching bronchus which deliver[s] to and receive[s] air from the alveolar regions of the lung." *Perkins*, column 6, lines 34 -39. In light of the explicit definition of "air passage" in Perkins, a summary of human pulmonary anatomy is appropriate, in support of which the Applicant respectfully directs the Examiner to Exhibit A (Figure 1-2) depicting a schematic diagram of the human airway. As shown in Exhibit A, the left and right bronchi are the two main tubes of the lung that extend from the trachea and branch off within the lung to form secondary and tertiary bronchi. The bronchi further branch to form smaller bronchioles and terminal bronchioles. At the ends of the terminal bronchioles are the alveoli. Based on the explicit definition of "air passage" in Perkins, the Applicant respectfully asserts that the methods of Perkins are limited to sealing the lung at the bronchi before the lung branches into its substructure.

Using the fibrin sealant of Edwardson in the methods of Perkins might provide the skilled artisan with a method for occluding or sealing leaks in an air passage leading to the lung after collapse. Critically, for the reasons discussed in detail in the preceding section, the Applicant respectfully asserts that use of the fibrin sealant of Edwardson in the methods of Perkins would not result in or render "obvious to try" the lung volume reduction methods claimed by Applicant.

Further, one of ordinary skill in the art would not have had a reasonable expectation of success in developing the claimed lung volume reduction methods in light of the combination of Perkins and Edwardson. As discussed in detail in the preceding section, due to their understanding of "collateral ventilation", those of ordinary skill in the relevant art at the time the instant application was filed would not have viewed the methods for lung volume reduction taught by the combination of Perkins and Edwardson as effective in producing atelectasis, and preventing the targeted region of the lung from receiving air flow. Collateral ventilation is the pulmonary phenomenon whereby apparently isolated alveolar regions are ventilated through passages or channels that bypass standard airways. <u>Due to collateral ventilation a section of a lung targeted for volume reduction via occlusion at the level of an "air passage" as defined in Perkins still receives airflow due to the presence of auxiliary airways, thereby preventing atelectasis.</u>

Consequently, the Applicant respectfully contends that one of ordinary skill in the art would not have had a reasonable expectation of success in utilizing the methods taught by the combination of Perkins and Edwardson for lung volume reduction. Moreover, the Applicants respectfully contend that the teachings of Perkins, Edwardson and the Exhibits provided herewith would have led one of ordinary skill in the art to conclude that it would be *unreasonable* to expect success in developing the claimed methods. Accordingly, the Applicants respectfully assert that no colorable argument can be made that one of ordinary skill in the art would have had a reasonable expectation of success in developing the claimed methods for lung volume reduction at the time the instant application was filed.

Based on the foregoing, Applicant respectfully requests withdrawal of the claim rejections under 35 U.S.C. § 103(a) based on Perkins in view of Edwardson.

Regarding claims 2-12

Claims 2-12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins in view of Edwardson and further in view of Antanavich et al. (US 5,814,022).

The Applicant respectfully asserts that the skilled artisan would not arrive at the claimed invention based on the combination of Perkins, Edwardson, and Antanavich because the cited combination does not disclose or render "obvious to try" all of the limitations of the rejected claims.

The Applicant respectfully contends that the combination of Perkins, Edwardson, and Antanavich does not meet the legal standard for *prima facie* obviousness with respect to the amended claims. Antanavich discloses the design of an apparatus for accurately dispensing tissue sealants, one of which sealants may be "an adhesive protein solution having a fibrinogen content of from 3 to 12%." The Examiner asserts that it would have been obvious to one of skill in the art "to provide the composition of fibrinogen from 3-12%, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art."

As discussed in detail above, Perkins teaches optionally sealing or occluding an air passage leading to the collapsed region of the lung by "delivering a plug..., typically at [*sic*] partially hydrated collagen hydrogel..." ***after*** the lung has been collapsed by vacuum aspiration or the application of external force. The plug is delivered to the lung bronchus and used to seal the air passage leading to the target lung segment. *See Perkins*, column 9, lines 24-29; column 10, lines 37-58; and Figure 4C. Importantly, Perkins defines an "air passage" as a "segment of the branching bronchus which deliver[s] to and receive[s] air from the alveolar regions of the lung." *Perkins*, column 6, lines 34 -39. In light of the explicit definition of "air passage" in Perkins, a summary of human pulmonary anatomy is appropriate, in support of which the Applicant respectfully directs the Examiner to Exhibit A (Figure 1-2) depicting a schematic diagram of the human airway. As shown in Exhibit A, the left and right bronchi are the two main tubes of the lung that extend from the trachea and branch off within the lung to form secondary and tertiary bronchi. The bronchi further branch to form smaller bronchioles and terminal bronchioles. At the ends of the terminal bronchioles are the alveoli. Based on the explicit definition of "air passage" in Perkins, the Applicant respectfully asserts that the methods of Perkins are limited to sealing the lung at the bronchi before the lung branches into its substructure.

Edwardson discloses a fibrin sealant. The Applicant respectfully asserts that the only arguably relevant portion of Antanavich is the disclosure of an adhesive protein solution having a fibrinogen content from 3 to 12 %.

Critically, for the reasons discussed in detail in the preceding sections, the Applicant respectfully asserts that the combined disclosure of Perkins, Edwardson and Antanavich (e.g., use of Antanavich's adhesive protein solution having a fibrinogen content from 3 to 12 % in

combination with the fibrin sealant of Edwardson in the methods of Perkins) would not result in or render "obvious to try" the lung volume reduction methods claimed by Applicant. Specifically, the combination of Perkins, Edwardson and Antanavich teaches or renders "obvious to try" only delivering a plug (made of Edwardson's fibrin sealant and Antanavich's adhesive protein solution having a fibrinogen content from 3 to 12 %) to occlude an air passage leading to a region of the lung ***after*** the lung has been independently collapsed by vacuum aspiration or the application of an external force. Therefore, the combination of Perkins, Edwardson, and Antanavich does not teach or render "obvious to try" all of the limitations of the amended claims.

Further, one of ordinary skill in the art would not have had a reasonable expectation of success in developing the claimed lung volume reduction methods in light of the combination of Perkins, Edwardson and Antanavich. As discussed in detail in the preceding section, due to their understanding of "collateral ventilation", those of ordinary skill in the relevant art at the time the instant application was filed would not have viewed the methods for lung volume reduction taught by the combination of Perkins, Edwardson and Antanavich as effective in producing atelectasis, and preventing the targeted region of the lung from receiving air flow. Collateral ventilation is the pulmonary phenomenon whereby apparently isolated alveolar regions are ventilated through passages or channels that bypass standard airways. Due to collateral ventilation a section of a lung targeted for volume reduction via occlusion at the level of an "air passage" as defined in Perkins still receives airflow due to the presence of auxiliary airways, thereby preventing atelectasis.

Consequently, the Applicant respectfully contends that one of ordinary skill in the art would not have had a reasonable expectation of success in utilizing the methods taught by the combination of Perkins, Edwardson and Antanavich for lung volume reduction. Moreover, the Applicants respectfully contend that the teachings of Perkins, Edwardson, Antanavich and the Exhibits provided herewith would have led one of ordinary skill in the art to conclude that it would be *unreasonable* to expect success in developing the claimed methods. Accordingly, the Applicants respectfully assert that no colorable argument can be made that one of ordinary skill in the art would have had a reasonable expectation of success in developing the claimed methods for lung volume reduction at the time the instant application was filed.

Based on the foregoing, Applicant respectfully requests withdrawal of the claim rejections under 35 U.S.C. § 103(a) based on Perkins in view of Edwardson and Antanavich.

Double Patenting

Claims 1-13 and 15 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

claims 14, 15, 22, 23, 31, 55, and 60 of co-pending Application No. 10/069,307;

claims 1-18 of co-pending Application No. 10/649,232;

claims 1-11 of U.S. Patent No. 6,610,043;

claims 1-32 of U.S. Patent No. 6,682,520; and

claims 1-4 of U.S. Patent No. 7,300,428.

The Applicant believes that the Examiner's double patenting rejection based on "claims 1-18 of co-pending Application No. 10/649,232" reflects a typographical error, as Application No. 10/649,232 is the present application. The Applicants respectfully request that the Examiner hold in abeyance all obviousness-type double patenting rejections based on cited patents and application until allowable subject matter is indicated, at which point the Applicants will file one or more terminal disclaimers, if necessary.

Fees

The Applicants believe they have provided the required fees in connection with the filing of this paper. Nevertheless, the Commissioner is hereby authorized to charge any additional required fees to our Deposit Account, **No. 06-1448** reference **ATX-011.04**.

Conclusion

The Applicants believe that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to contact the undersigned.

Respectfully submitted,
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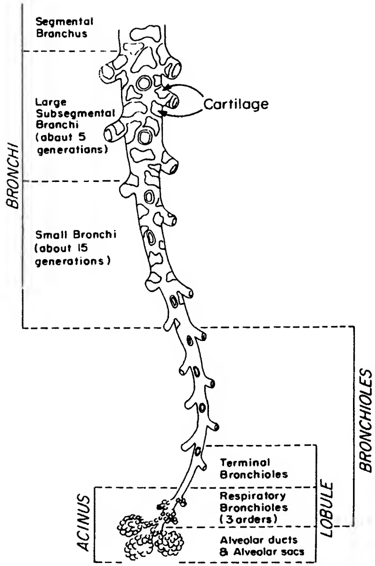
Date: March 26, 2009

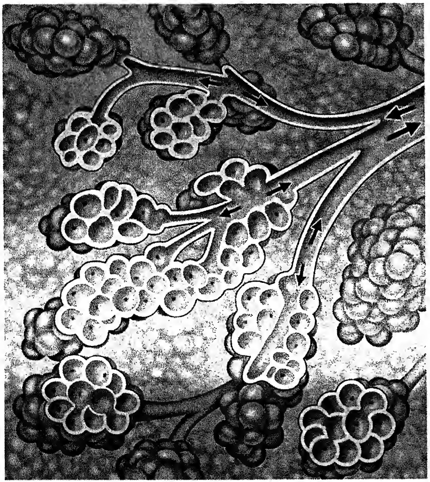
FIGURE 1-2. SCHEMATIC DIAGRAM OF THE AIRWAY

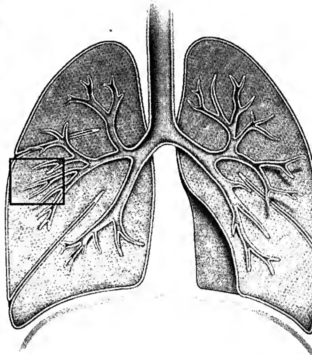


Schematic diagram of the airway. Progressive subdivision of the tracheo-bronchial tree illustrating both conducting airways and respiratory unit. From E.P. Horvath Jr., S.M. Brooks, and J.L. Hankinson [1981]. Manual of Spirometry in Occupational Medicine, U.S. Department of Health and Human Services, p. 5. (6).

Normal Lung Without Collateral Ventilation

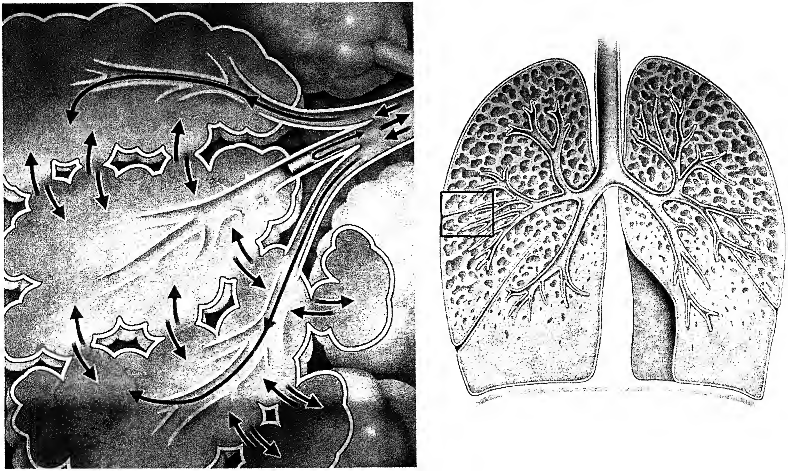
Healthy alveolar regions are not interconnected





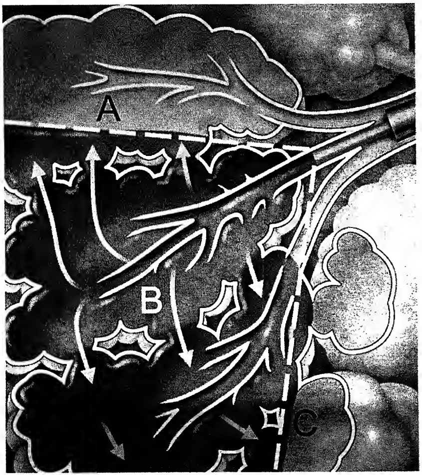
Emphysematous Lung With Collateral Ventilation

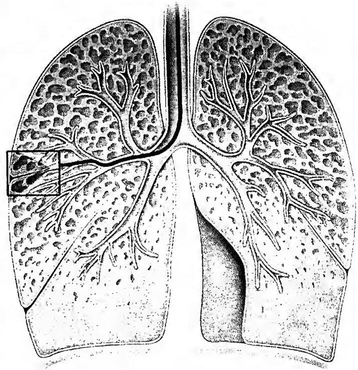
A bronchial plug is not effective because air flows between interconnected diseased alveolar regions



Emphysematous Lung With Collateral Ventilation

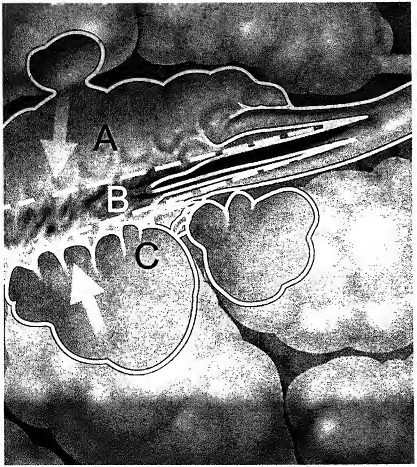
Administration of composition into diseased alveolar regions is therapeutically effective because collateral ventilation is rendered structurally irrelevant

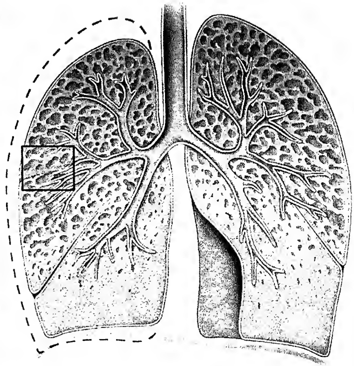




Emphysematous Lung With Collateral Ventilation

Lung volume is reduced as a result of administration of composition into diseased alveolar regions because collateral ventilation was rendered structurally and therapeutically irrelevant





Effect of Bronchoscopic Lung Volume Reduction on Dynamic Hyperinflation and Exercise in Emphysema

Nicholas S. Hopkinson, Tudor P. Toma, David M. Hansell, Peter Goldstraw, John Moxham, Duncan M. Geddes, and Michael I. Polkey

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Endobronchial valve placement improves pulmonary function in some patients with chronic obstructive pulmonary disease, but its effects on exercise physiology have not been investigated. In 19 patients with a mean (SD) FEV_1 of 28.4 (11.9)% predicted, studied before and 4 weeks after unilateral valve insertion, functional residual capacity decreased from 7.1 (1.5) to 6.6 (1.7) L ($p = 0.03$) and diffusing capacity rose from 3.3 (1.1) to 3.7 (1.2) mmol · minute^{-1} · kPa^{-1} ($p = 0.03$). Cycle endurance time at 80% of peak workload increased from 227 (129) to 315 (195) seconds ($p = 0.03$). This was associated with a reduction in end-expiratory lung volume at peak exercise from 7.6 (1.6) to 7.2 (1.7) L ($p = 0.03$). Using stepwise logistic regression analysis, a model containing changes in transfer factor and resting inspiratory capacity explained 81% of the variation in change in exercise time ($p < 0.0001$). The same variables were retained if the five patients with radiologic atelectasis were excluded from analysis. In a subgroup of patients in whom invasive measurements were performed, improvement in exercise capacity was associated with a reduction in lung compliance ($r^2 = 0.43$; $p = 0.03$) and isotime esophageal pressure–time product ($r^2 = 0.47$; $p = 0.03$). Endobronchial valve placement can improve lung volumes and gas transfer in patients with chronic obstructive pulmonary disease and prolong exercise time by reducing dynamic hyperinflation.

Keywords: bronchoscopic lung volume reduction; chronic obstructive pulmonary disease; diaphragm; dynamic hyperinflation

Patients with advanced chronic obstructive pulmonary disease (COPD) frequently experience exertional breathlessness despite optimal medical therapy. In selected patients lung volume reduction surgery (LVRS) has been shown to improve mortality, exercise capacity, and quality of life (1–3). However, it is associated with significant morbidity and an early mortality rate of about 5% (1, 2). For these reasons and because the procedure poses an unacceptable risk in patients with the most severe disease (1, 4), alternatives have been sought including bronchoscopic lung volume reduction (BLVR). This involves obstructing the airways that supply the most hyperinflated, emphysematous parts of the lung. The rationale for this approach is that endobronchial obstruction should cause these areas to collapse as a result of absorption atelectasis. By reducing lung volumes, symptoms could be improved without recourse to surgery. The technique was first performed with airway blockers (5) and subsequently our group (6) and others (7, 8) have described early experience with the use of endobronchially placed valves. However, our experience suggests that lobar collapse is not necessary for clinically apparent benefit to occur and we reasoned therefore that other physiologic mechanisms must operate.

A key element in ventilatory limitation of exercise in COPD is the development of dynamic hyperinflation, in which expiratory flow limitation leads to a progressive increase in end-expiratory lung volume during exercise and consequently restricts the tidal volume that can be achieved (9). Reductions in dynamic hyperinflation have been demonstrated after treatment with bronchodilators (10–12) and after lung volume reduction surgery or bullectomy (13). BLVR could be expected to reduce dynamic hyperinflation either by causing the worst affected areas of lung to collapse or by excluding them from ventilation. In the presence of significant atelectasis BLVR should lead to a better matching of lung and chest wall dimensions, thus increasing available vital capacity as occurs after LVRS (14). By collapsing the most compliant areas of lung this should lead to an increase in lung elastic recoil at any given lung volume, reducing airflow obstruction.

In the absence of atelectasis BLVR might still have benefits, first by reducing physiological dead space, which would improve the efficiency of ventilation, and second by reducing the dynamic hyperinflation that occurs at higher levels of ventilation by diverting airflow to less obstructed areas of lung.

Therefore the aim of the present study was to investigate the effect of endobronchial valve placement on exercise capacity in patients with emphysema and to relate this to changes in dynamic hyperinflation assessed through changes in end-expiratory lung volumes. Some of the results of these studies have been reported previously in abstract form (15).

METHODS

Patients with COPD consistent with the GOLD guidelines (16) entered the study if they had significant dyspnea despite optimal medical therapy including pulmonary rehabilitation; presented a heterogeneous pattern of disease with a target area identified by computed tomography (CT) scanning and ventilation perfusion scintigraphy (6); and were either considered too great a risk for LVRS (1, 4), or declined the surgery. The Royal Brompton Hospital (London, UK) Research Ethics Committee approved the study and patients gave their informed consent. Some data from the first eight patients in our series have been published previously (6).

Endobronchial occlusion was performed with one-way valves (Emphasys Medical, Redwood City, CA) made of nitinol and silicone (*see* Figures E1 and E2 in the online supplement), placed to occlude segmental bronchi leading to the most affected area of lung. All procedures were unilateral. Initially, valves were inserted on a single occasion under general anesthesia (6, 17). Subsequently some procedures were performed with sedation only and some of these were staged, with

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This manuscript has an online supplement, which is accessible from this issue's table of contents at www.thoracic.org

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Internet address: www.atsjournals.org

valves being inserted on two separate occasions 1 to 2 weeks apart. Measurements were made in the week preceding and 4 weeks after valve insertion had been completed. A radiologist blinded to clinical outcome assessed CT evidence of atelectasis, defined as changes in the position of interlobar fissures adjacent to the targeted area.

Quality of life was assessed on the basis of St George's Respiratory Questionnaire and the Short Form-36.

Pulmonary and Respiratory Muscle Function

Spirometry, gas transfer, and lung volumes assessed by body plethysmography were measured with a CompactLab system (Jaeger, Hoechberg, Germany). Pa_{O_2} and Pa_{CO_2} were measured in arterialized earlobe capillary samples. Static lung compliance was measured by an interrupter technique during a relaxed expiration from total lung capacity (TLC).

In all subjects we measured maximal static inspiratory (PI_{max}) and expiratory (PE_{max}) mouth pressures (18) as well as maximal sniff nasal pressure (Pn,sn) (19). When patients consented to and were able to tolerate the placement of catheter-mounted balloons, esophageal and gastric pressures were determined and transdiaphragmatic pressure was calculated (19). In these patients sniff transdiaphragmatic pressure (Pdi,sn) and the response to bilateral anterolateral magnetic phrenic nerve stimulation (Pdi,tw) were also determined (20).

Exercise Testing

Patients performed endurance cycle ergometry at 80% of the maximal workload achieved on a previous incremental test before and after BLVR, with inspiratory capacity (IC) maneuvers performed every minute to assess changes in end-expiratory lung volume. Both peak and isotime values were compared. Isotime was defined as the final 30-second period achieved on the shorter of the two tests. Leg and breathing discomfort were assessed on the basis of the Borg scale.

In some patients we recorded esophageal and gastric pressures during exercise, calculating esophageal and diaphragmatic pressure–time product (PTP) (21, 22). Further methodologic details are given in the online supplement.

Statistical Analysis

The primary end point in this study was change in cycle endurance time (T_{lim}) 4 weeks after the procedure as a continuous variable. In addition, patients with an increase of both 60 seconds and 30% were defined *a priori* as "improvers." Changes from baseline were assessed using appropriate test for paired comparisons. Baseline predictors and correlates of improvement in T_{lim} were sought, using linear regression and then stepwise logistic regression analysis to identify which parameters had an independent effect.

RESULTS

Procedures and Complications

Nineteen subjects (16 men) were studied. Baseline characteristics are given in Table 1. Details of the procedure performed in each subject, as well as the presence of radiologic atelectasis and individual changes in cycle endurance time and resting inspiratory capacity, are given in Table E1. All but 1 patient were taking inhaled steroids, 12 were taking long-acting β_2 agonists, 7 were taking oral theophyllines, 3 were taking regular oral prednisolone (less than 10 mg/day), 11 used a nebulizer, and 2 were receiving long-term oxygen therapy. The median (range) number of exacerbations requiring antibiotics in the preceding year was 2 (0–7).

There were no immediate complications related to the procedure itself. Two patients, both of whom had radiologic evidence of volume reduction, developed ipsilateral pneumothoraces: one at 2 days, which required intercostal drainage, and one at 4 weeks, which was small and resolved without intervention. There were no episodes of obstructive pneumonia. In five patients there was a transient worsening of symptoms consistent with an acute exacerbation in the early period after the procedure; these patients were treated with oral antibiotics. One subject developed

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS

Baseline Characteristic	Value
Sex, M/F	16/3
Age, yr	58.7 (8.7)
BMI, kg · m^{-2}	23.3 (4.1)
FEV_1, % predicted	28.4 (11.9)
TL_{CO}, % predicted	35.9 (10.9)
TLC, % predicted	139.3 (15.6)
RV, % predicted	260.5 (68.4)
FRC, % predicted	208.9 (38.9)
Peak workload, W	49.0 (18)
Peak $\dot{V}O_2$, L · min^{-1}	0.84 (0.22)
Peak $\dot{V}CO_2$, L · min^{-1}	0.78 (0.21)
Peak $\dot{V}E$, L · min^{-1}	29.7 (8.1)
Peak $\dot{V}E$, % predicted	99.8 (22.2)

Definition of abbreviations: BMI = body mass index; F = female; M = male; RV = residual volume; TLC = total lung capacity; TL_{CO} = transfer factor for carbon monoxide; $\dot{V}CO_2$ = carbon dioxide production; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen consumption.

Exercise parameters are values obtained during symptom-limited incremental cycle ergometry.

Values represent means (SD).

Clostridium difficile diarrhea, presumably resulting from prophylactic antibiotic treatment, and one patient tripped at home, sustaining a rib fracture. In these patients postprocedure tests were delayed until they had recovered from these events.

Radiologic evidence of atelectasis was present in five subjects (26%). In the group as a whole there were significant improvements in airflow obstruction, lung volumes, and transfer factor for carbon monoxide (TL_{CO}) (Table 2).

Exercise Performance

In the group overall there was a 39% improvement in mean cycle endurance exercise time from 227 (129) to 315 (195) seconds ($p = 0.03$), giving a mean ΔT_{lim} of +88 (167) seconds (Figure 1). Nine patients (47%) met the 60-second and 30% increase criteria considered to represent a clinically significant benefit and were defined as improvers.

Whole group mean changes in peak and isotime exercise parameters are given in Table E2. At peak exercise, end-expiratory lung volume (EELV) was reduced from 7.60 (1.6) to 7.18 (1.7) L ($p = 0.03$) and at isotime from 7.47 (1.5) to 6.97 (1.7) L ($p = 0.05$) with nonsignificant trends toward improvement in other parameters. If patients with atelectasis were excluded, the improvement in T_{lim} among the remaining 14 patients was no longer significant: preprocedure, 246 (143) seconds; postprocedure, 285 (179) seconds ($p = 0.2$).

Improvement in endurance time was associated with improvements in lung function, measures of dynamic hyperinflation and esophageal pressure–time product, as well as a reduction in static compliance (Table 3). Using stepwise regression analysis including all the variables listed in Table 3, only change in resting inspiratory capacity and ΔTL_{CO} were retained as independent predictors, producing an equation that explained 81% of the variation in ΔT_{lim} ($p < 0.0001$): $\Delta T_{lim} = -1.4 + 153 \times (\Delta TL_{CO}$ [mmol · min^{-1} · kPa^{-1}]) + 257 × (Δ resting IC [L]). If patients with atelectasis were excluded, again only the same two variables were retained in the model ($r^2 = 0.61$; $p = 0.002$).

The results of a binary analysis comparing "improvers" with "nonimprovers" are given in Table 4. At isotime the improvers had a reduction in dyspnea and respiratory rate as well as highly significant reductions in lung volumes, with a decrease in EELV of 1.01 (0.8) L compared with an increase of 0.14 (0.5) L ($p = 0.002$) among the nonimprovers.

TABLE 2. CHANGES IN PULMONARY FUNCTION AND RESPIRATORY MUSCLE STRENGTH AFTER BRONCHOSCOPIC LUNG VOLUME REDUCTION

	Baseline	4 Weeks	p Value (t *Test*)
FEV_1, L	0.90 ± 0.4	0.99 ± 0.4	0.071
FEV_1, % predicted	28.4 ± 11.9	31.5 ± 13.2	0.047*
VC, L	3.38 ± 0.96	3.50 ± 0.94	0.4
FEV_1/VC ratio	27.2 ± 9.4	29.1 ± 9.7	0.046*
PEFR, % predicted	39.6 ± 14.1	44.3 ± 18.1	0.033*
TLC, L	9.06 ± 1.5	8.75 ± 1.5	0.03*
TLC, % predicted	139.3 ± 15.6	135.58 ± 17.6	0.043*
RV, L	5.80 ± 1.7	5.23 ± 1.6	0.099
RV, % predicted	260.5 ± 68.4	240.4 ± 64.5	0.24
RV, % TLC	63.18 ± 12.0	58.80 ± 11.0	0.12
FRC, L	7.09 ± 1.5	6.61 ± 1.7	0.029*
FRC, % predicted	209.8 ± 38.9	195.7 ± 42.3	0.021*
TL_{CO}	3.32 ± 1.1	3.73 ± 1.2	0.026*
TL_{CO}, % predicted	35.94 ± 10.9	40.91 ± 11.9	0.016*
VA	4.99 ± 1.2	5.13 ± 1.0	0.98
VA, % predicted	84.8 ± 18.0	87.4 ± 14.2	0.053
TL_{CO}/VA	0.68 ± 0.2	0.73 ± 0.2	0.034*
TL_{CO}/VA, % predicted	46.0 ± 13.5	49.6 ± 14.6	0.018*
PI_{max}, cm H_2O	62.0 ± 21.8	64.2 ± 17.3	0.43
PE_{max}, cm H_2O	96.4 ± 30.5	111.0 ± 26.8	0.004*
WMEP, cm H_2O	92.4 ± 32.8	120.3 ± 37.6	0.003*
Pn,sn, cm H_2O	66.0 ± 23.3	67.7 ± 17.3	0.7
Pdi,sn, cm H_2O	92.1 ± 22.0	99.3 ± 23.1	0.93
Pes,sn, cm H_2O	72.8 ± 24.0	77.3 ± 18.1	0.51
Cough Pgas, cm H_2O	267.7 ± 60.9	267.0 ± 48.3	0.88
Pdi,tw, cm H_2O	14.9 ± 6.3	17.1 ± 6.6	0.28

Definition of abbreviations: Pdi,sn = sniff transdiaphragmatic pressure; Pdi,tw = twitch transdiaphragmatic pressure; PEFR = peak expiratory flow rate; PE_{max} = maximal expiratory pressure; Pes,sn = sniff esophageal pressure; Pgas = gastric pressure; PI_{max} = maximal inspiratory pressure; Pn,sn = sniff nasal pressure; RV = residual volume; TLC = total lung capacity; TL_{CO} = transfer factor for carbon monoxide; VA = alveolar volume by helium dilution; WMEP = whistle maximal expiratory pressure.

Values represent means ± SD.

* $p < 0.05$.

Changes in exercise capacity were not significantly associated with change in isotime heart rate or oxygen pulse ($\dot{V}O_2$/heart rate), or with changes in inspiratory muscle strength. Pdi,tw rose by 28.0 (31.6)% in the improvers but fell by 2.3 (23.9)% in nonimprovers, but this difference did not quite reach significance (p = 0.07).

Improvement in T_{lim} was weakly associated with reduction (improvement) in the activity domain of the St. George's Respiratory Questionnaire ($r^2 = 0.23$; p = 0.04). Other parameters were not significantly correlated.

Pressure measurements during exercise were available in 10 patients, that is, 4 improvers (1 with atelectasis) and 6 nonimprovers (1 with atelectasis). In the group as a whole, isotime ventilatory efficiency tended to improve: $\dot{V}T$/Pes,sw: preprocedure, 35.4 (23.1) ml/cm H_2O; postprocedure, 44.3 (24.4) ml/cm H_2O (p = 0.08); and $\dot{V}E$/PTPes: preprocedure, 0.09 (0.05) L/cm H_2O · second · minute^{-1}; postprocedure, 0.10 (0.06) L/cm H_2O · second · minute^{-1} (p = 0.052).

Role of Atelectasis

As expected, radiologic atelectasis was significantly associated with improvement in exercise capacity, with a ΔT_{lim} of +225 (221) seconds (improvers) compared with +40 (117) seconds (nonimprovers) (p = 0.03). Four of five of these patients were classified as improvers, the exception being the patient who had a pneumothorax requiring intercostal drainage. Patients with atelectasis also tended to have greater improvements in lung

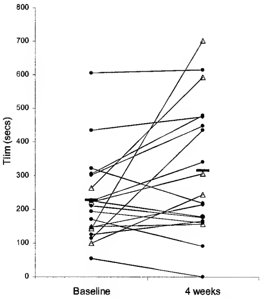

Figure 1. Mean endurance T_{lim} at 80% maximal workload increased from 227 (129) to 315 (195) seconds (p = 0.03). Patients who developed atelectasis are represented by *open triangles.*

function: FEV_1, +0.29 (0.23) versus +0.02 (0.17) L (p = 0.01); resting IC, +0.38 (0.38) versus +0.06 (0.34) L (p = 0.09); RV, –1.0 (1.6) versus –0.2 (0.7) L (p = 0.16); and TL_{CO}, +0.79 (0.79) versus +0.15 (0.35) (p = 0.03) together with a trend toward a greater reduction in isotime EELV, –1.0 (1.4) versus –0.2 (0.4) L (p = 0.07), although the small numbers involved prevented some of these differences from achieving statistical significance (*see* Table E4).

The only parameter measured at baseline that predicted the development of radiologic atelectasis was the body mass index (BMI), which was higher among those in whom it occurred: 28.3 (2.9) kg · m^{-2} versus 21.6 (2.9) kg · m^{-2} (p = 0.0004).

Static Lung Compliance

Values were obtained on two occasions in 10 patients (6 improvers and 4 with atelectasis). Data were unavailable either because patients did not have esophageal pressure catheters in place or because they were unable to perform a satisfactory relaxed expiration from TLC. Mean static lung compliance did not change significantly, being 4.1 (0.8) L/kPa pre-BLVR and 4.0 (0.08) L/kPa post-BLVR (p = 0.6). Baseline lung compliance did not predict improvement after BLVR, but reduction in compliance was significantly correlated with improvement in exercise capacity ($r^2 = 0.43$; p = 0.03), although this was not retained as an independent predictor of change in multivariate analysis.

Respiratory Muscle Strength

Invasive measurements of respiratory pressures were available for 14 patients. Two were unable to tolerate passage of the pressure catheters and three declined to swallow them a second time. In one further subject magnetic phrenic nerve stimulation was not performed because he had an implanted cardiac pacemaker. In the group as a whole there was no significant change in inspiratory muscle strength measured either volitionally or nonvolitionally and changes in respiratory muscle strength did not correlate with changes in endurance time. There was a significant increase in maximal expiratory mouth pressures but not in cough gastric pressure (Table 2). There was a good correlation between

TABLE 3. UNIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH CHANGE IN CYCLE ENDURANCE TIME AFTER BRONCHOSCOPIC LUNG VOLUME REDUCTION

	All Patients		Patients without Atelectasis	
	r^2 Value	p Value	r^2 Value	p Value
ΔFEV$_1$	0.43	0.002	0.22	0.08
ΔVC	0.50	0.001*	0.29	0.06
ΔTL$_{CO}$	0.62	< 0.0001*	0.29	0.15
ΔTLC	0.53	0.0006*	0.25	0.08
ΔRV	0.56	0.0003*	0.33	0.04*
ΔIC (at rest)	0.59	0.0001*	0.45	0.009*
ΔCstat	0.43	0.03*	0.57	0.049*
ΔEELV (isotime)	0.62	0.0001*	0.61	0.002*
ΔIRV (isotime)	0.34	0.011*	0.48	0.009*
Δ$\dot{V}$T (isotime)	0.40	0.005*	0.11	0.27
ΔRR (isotime)	0.41	0.004*	0.52	0.005*
ΔBorg dyspnea score (isotime)	0.40	0.005*	0.25	0.08
ΔBorg leg discomfort score (isotime)	0.06	0.32	0.37	0.03*
ΔPn,sn	0.11	0.17	0.01	0.7
	Subgroup of Patients (*n* = *10*)		Subgroup of Patients (*n* = *8*)	
ΔPTPes (isotime)	0.43	0.03*	0.21	0.3
Δ$\dot{V}$T/Pes,sw (isotime)	0.56	0.01*	0.41	0.09
ΔPEEP$_i$ (isotime)	0.22	0.17	0.38	0.1
ΔPes,sw (isotime)	0.44	0.04*	0.27	0.2

Definition of abbreviations: Cstat = static lung compliance; IC = inspiratory capacity; EELV = end-expiratory lung volume; IRV = inspiratory reserve volume; PEEP$_i$ = intrinsic positive end-expiratory pressure; Pes,sw = esophageal pressure swing; Pn,sn = sniff nasal pressure; PTPes = esophageal pressure–time product; RV = residual volume; RR = respiratory rate; TLC = total lung capacity; TL$_{CO}$ = transfer factor for carbon monoxide; $\dot{V}$T = tidal volume.

The Δ values represent change from baseline 4 weeks after BLVR. Only ΔIC (at rest) and ΔTL$_{CO}$ were retained as independent variables by stepwise logistic regression analysis.

*$p < 0.05$.

change in twitch transdiaphragmatic pressure and change in functional residual capacity ($r^2 = 0.67$; $p < 0.001$) with an increase in Pdi,tw equivalent to 4.5 cm H_2O for every liter reduction in functional residual capacity (FRC) (Figure 2).

Factors Predicting Improvement in Exercise Capacity

A similar analysis was performed to determine which factors at baseline predicted improvement after BLVR (Table 5). Stepwise regression analysis was applied to a model containing BMI, VC % predicted, FEV$_1$, RV/TLC, peak minute ventilation, respiratory rate and tidal volume, Pn,sn, Borg dyspnea and leg fatigue scores, as well as percentage reduction in inspiratory capacity. Only percent predicted vital capacity and respiratory rate were retained: ΔT_{lim} = 24.5 (RR) – 3.3 (VC % predicted) – 294 (r^2 = 0.62; p = 0.0004).

Although the difference was not significant it is interesting to note that the mean change in endurance time in those reporting limitation by leg fatigue alone or a mixture of leg fatigue and breathlessness (n = 6) was –1.7 (70.1) seconds compared with an increase of 129.9 (183.4) seconds in those reporting limitation by breathlessness alone (p = 0.1).

DISCUSSION

In this study we found that endobronchial valve placement improved mean exercise capacity and reduced dynamic hyperinflation in patients with COPD. The response was heterogeneous, with 47% of patients having a clinically significant improvement in exercise performance. Radiologic atelectasis occurred in only five patients. Improvements in exercise time were independently associated both with improvements in diffusing capacity and with reductions in static lung volumes, both in the presence and absence of atelectasis. Improvement post-BLVR was associated with a lower vital capacity and higher respiratory rate during peak exercise measured at baseline.

Before discussing the significance of our findings a number of methodologic issues need to be addressed. The main outcome measure in this study was change in cycle endurance time at 80% of peak workload, which was analyzed as a continuous variable. Cycle endurance time has been shown to be highly reproducible in patients with COPD (11, 23), although there is no widely accepted definition of what constitutes a clinically significant change in endurance time at any given workload. However, on the basis of other studies that have looked at the effect of bronchodilators or LVRS in COPD (11, 12, 24) the scale of improvement observed is unlikely to have occurred as a consequence of natural variation or a placebo effect. The comparison of physiological parameters measured at isotime also makes a placebo effect unlikely. Because the response was heterogeneous, we have also presented the data in a binary fashion comparing changes in those who did or not improve. This definition, although arbitrary, was determined *a priori* on the basis of changes described in other studies (11, 12, 24) and serves to highlight differences between the two populations.

A further limitation of the present study is that it was not possible to obtain a full range of invasive measurements in all subjects. This is to be expected because these were patients with significant disease and some people find passage of esophageal pressure catheters too uncomfortable to tolerate. However, we think that this is unlikely to have rendered these data untypical of the group as a whole because in the subgroup where pressure measurements during exercise were available, the proportion both of improvers (4 of 10) and of patients developing atelectasis (2 of 10) was similar to the group as a whole.

The absence of atelectasis could have occurred because there was incomplete blockage of the relevant segment, or because of

TABLE 4. COMPARISON OF CHANGES IN ISOTIME EXERCISE PARAMETERS IN PATIENTS WITH OR WITHOUT AN IMPROVEMENT IN EXERCISE ENDURANCE TIME

Change in Isotime Value	Nonimprovers (*n* = 10)	Improvers (*n* = 9)	p Value (t *Test*)
T_{lim}, s	−18.6 ± 36	+130.8 ± 125	0.002*
IC, L	−0.20 ± 0.4	+0.51 ± 0.4	0.002*
EELV, L	+0.14 ± 0.5	−1.01 ± 0.8	0.002*
IRV, L	−0.14 ± 0.4	+0.34 ± 0.3	0.006*
$\dot{V}_E$, L · min^{-1}	+0.61 ± 5.0	+0.66 ± 3.8	0.98
RR, min^{-1}	+1.0 ± 3.3	−3.3 ± 3.5	0.01*
$\dot{V}_T$, L	−0.11 ± 0.2	+0.17 ± 0.2	0.06
Borg leg discomfort score	−0.28 ± 1.5	−0.89 ± 1.2	0.36
Borg breathlessness score	+0.72 ± 1.7	−1.7 ± 2.0	0.01*
	Subgroup of Patients (*n* = 6)	Subgroup of Patients (*n* = 4)	
PTPdi, cm H_2O · s · min^{-1}	+26.5 ± 77.5	−29.0 ± 139.9	0.44
PTPes, cm H_2O · s · min^{-1}	+8.7 ± 31.3	−65.4 ± 65.1	0.004*
Peak expiratory Pes, cm H_2O	−0.6 ± 4.7	−20.3 ± 10.6	0.004*
Peak inspiratory Pes, cm H_2O	−1.9 ± 1.8	+2.2 ± 1.8	0.008*
Pes,sw, cm H_2O	+1.5 ± 5.2	−23.3 ± 13.4	0.003*
$PEEP_i$, cm H_2O	−0.5 ± 3.3	−4.7 ± 1.5	0.046*
$\dot{V}_T$/Pes,sw, ml · cm H_2O^{-1}	+1.0 ± 10.4	+20.7 ± 9.6	0.016*
$\dot{V}_E$/PTPes, L/cm H_2O · s · min^{-1}	+0.05 ± 0.1	+0.02 ± 0.1	0.052

Definition of abbreviations: EELV = end-expiratory lung volume; IC = inspiratory capacity; IRV = inspiratory reserve volume; peak expiratory Pes = mean maximal expiratory esophageal pressure; peak inspiratory Pes = mean most negative inspiratory pressure; $PEEP_i$ = intrinsic positive end-expiratory pressure; Pes,sw = difference between the two in each respiratory cycle; PTPes = esophageal pressure–time product; RR = respiratory rate; $\dot{V}_E$ = minute ventilation; $\dot{V}_E$/PTPes = minute ventilation divided by esophageal pressure–time product; $\dot{V}_T$ = tidal volume.

Improvement was defined as an at least 60-second increase in endurance time (T_{lim}) on a cycle ergometer at 80% of maximal workload before BLVR.

Values represent means ± SD.

* $p < 0.05$.

incomplete valve closure, but this did not appear to be the case when the valves were inspected visually. Because atelectasis did not occur in the majority of patients despite the apparent occlusion of all segments this suggests that there must have been significant interlobar collateral ventilation. A frequent incidence of incomplete fissures in postmortem studies of patients with emphysema has been noted previously (25) and increased collateral ventilation in this condition, which is likely in the presence of relatively lower resistance collateral channels and marked time constant inequalities (26), has been measured by a helium dilution technique (27). Interlobar collaterals have been demonstrated in 12 of 21 explanted lungs from patients with severe emphysema undergoing lung transplantation (28). No clinical factor appeared to predict the presence of these collaterals, which is consistent with our observation that no pre-BLVR factor except for BMI predicted atelectasis. It is possible also that a degree of atelectasis did occur that was too subtle to be apparent on CT.

The observation that atelectasis was more likely to occur in patients with a higher BMI is intriguing. It was not retained as an independent correlate of improvement in exercise capacity. It is not obvious by what mechanism this could influence the presence of collateral ventilation. It may be a chance finding, but will be an important factor to consider in future studies.

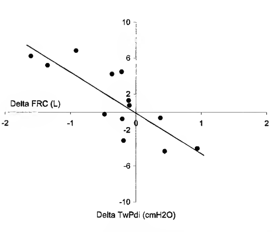

Figure 2. Change in twitch transdiaphragmatic pressure (Pdi,tw) plotted against change in functional residual capacity (FRC) 4 weeks after BLVR ($r^2 = 0.7$; $p < 0.001$).

Change in Pulmonary Function after BLVR

The pattern of change in lung volumes that we observed is similar to that seen in LVRS, where the reduction in RV is larger than the reduction in TLC, producing an increase in vital capacity, although the net change in VC did not reach statistical significance in this study. In LVRS actual lung tissue is removed, which, depending on the heterogeneity of emphysema, may change the elastic recoil properties of the lung. In addition, areas of healthy lung will be decompressed, allowing the recruitment of functional airways, alveoli, and capillaries. After BLVR, if atelectasis occurs the effect should be similar, and the changes in lung volumes that we observed in these patients were of a similar order of magnitude to those seen after LVRS (1). In the absence of frank atelectasis the targeted area will still be relatively excluded from ventilation. Placement of the valve means that the airway is either obstructed or at least has a high inspiratory resistance such that airflow is diverted to areas of healthier lung that are more able to empty. It remains surprising that reduction in static lung volumes occurred in the absence of radiologic atelectasis. We would acknowledge that the radiologic technique

TABLE 5. UNIVARIATE ANALYSIS OF BASELINE FACTORS ASSOCIATED WITH IMPROVEMENT IN T_{lim}

	All Patients	
	r^2 Value	p Value
Baseline parameters		
Weight, kg	0.243	0.03*
BMI, kg · m^{-2}	0.174	0.08
QMVC, kg	0.202	0.07
Baseline lung function		
FEV_1, % predicted	0.03	0.5
VC, % predicted	0.16	0.09
RV, % predicted	0.00	0.8
TL_{CO}, % predicted	0.00	0.8
Baseline peak exercise parameters		
Workload, W	0.04	0.4
$\dot{V}CO_2$, L · min^{-1}	0.01	0.7
$\dot{V}O_2$, L · min^{-1}	0.01	0.7
$\dot{V}E$, % predicted	0.21	0.051
RR, min^{-1}	0.45	0.002*
$\dot{V}T$, L	0.03	0.5
Reduction in IC, %	0.03	0.8
PTPes, cm H_2O · s · min^{-1}	0.35	0.07
$PEEP_i$, cm H_2O	0.14	0.29

Definition of abbreviations: BMI = body mass index; IC = inspiratory capacity; $PEEP_i$ = intrinsic positive end-expiratory pressure; PTPes = esophageal pressure–time product; QMVC = quadriceps maximal voluntary contraction; RR = respiratory rate; RV = residual volume; TL_{CO} = transfer factor for carbon monoxide; VC = vital capacity; $\dot{V}CO_2$ = carbon dioxide production; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen consumption; $\dot{V}T$ = tidal volume.

Using stepwise logistic regression analysis, only VC (% predicted) and respiratory rate were retained in the model (r^2 = 0.62; p = 0.0004).

* $p < 0.05$.

might have been insufficiently sensitive, particularly because it is made near to TLC. Ideally we would have performed scans at end expiration as well, to clarify this further. A possible explanation for this discrepancy between radiologic and plethysmographic findings is that in patients with emphysema, lung volumes may be overestimated because of a damping of alveolar pressure changes as measured by changes in mouth pressure. Because the valves were placed to occlude the worst affected areas of lung, which contribute most to this artifact, effectively converting them to bullae, the measured volume may have appeared to decrease without any actual reduction in lung volume.

Transfer factor for carbon monoxide increased significantly after valve insertion, and change in this parameter was a powerful independent predictor of improvement in exercise capacity. The mechanism of improvement is unclear. Single-breath assessment of TL_{CO} involves a rapid inspiratory maneuver that may mimic dynamic flow effects during exercise more closely than measurement of static lung volumes. By excluding the worst affected segments of lung from ventilation, endobronchial valve placement would be expected to reduce inhomogeneity of gas mixing, diverting inspired gas to areas that are better perfused. In addition, where atelectasis occurs it may also permit the recruitment of previously "compressed" alveolar units in relatively healthier lung. There may also have been an increase in pulmonary capillary volume due to an improvement in cardiac function (as has been observed after LVRS [29]) either through a reduction in intrathoracic pressure swing or, again, because of a recruitment of additional capillaries in areas of compressed lung that are able to reexpand. Finally, the target area of lung, being the most emphysematous, would be expected to have the slowest time constants and might therefore have been contaminating the "alveolar" part of the sample during expiration preprocedure. This final mechanism, although reflecting emphysematous pathophysiology, might more properly be thought of as a measurement error.

LVRS, possibly because the technique inevitably requires the removal of some relatively normal lung tissue, has not been found to improve TL_{CO} in a number of studies (1, 30) although this has not been a universal finding (31, 32). This distinction may represent an important area of difference between the two techniques.

Dynamic hyperinflation is central to exercise limitation in COPD (10, 11). In the present study, improvement in exercise capacity was associated with lower lung volumes, less dyspnea, and reduced respiratory pressures at isotime, consistent with previous work examining the effects of bronchodilators (33). Similar improvements in mechanical coupling have been demonstrated at rest after LVRS (34–36) and after exercise training (37). Changes in parameters of dynamic hyperinflation were not retained as independent predictors of improvement in exercise capacity when changes in resting inspiratory capacity and TL_{CO} were included in the model, however. Change in resting IC has previously been shown to be the strongest correlate of improvements in exercise capacity after treatment with bronchodilators (38). The increased IC at rest allows the recruitment of functional airways and allows an increased tidal volume. Dynamic hyperinflation depends on minute ventilation and airflow obstruction. Among improvers, minute ventilation at isotime was unchanged but the pattern of ventilation was altered, with a reduction in respiratory rate and an increase in tidal volume.

In the subgroup of patients with invasive measurements we observed an association between reduction in isotime PTPes and improvement in T_{lim}. PTPdi did not change significantly. This is consistent with the previous observation that in patients with COPD the diaphragm is mechanically disadvantaged, such that PTPdi tends to plateau despite increases in neural drive at higher levels of ventilation during exercise (22, 39). In particular there was a reduction in expiratory pressure generation. Expiratory pressure generation cannot improve ventilation in patients with expiratory flow limitation and the change observed is likely to improve overall efficiency both by reducing the oxygen cost of breathing and possibly by improving cardiac function. On the latter point it should be noted that we did not find any change in either heart rate or oxygen pulse after BLVR. These are, however, both relatively crude markers of cardiac function and it is possible that pulmonary artery measurements would have revealed differences. Interestingly, applying noninvasive ventilatory support only in the inspiratory phase of breathing has previously been shown to reduce expiratory pressure generation during exercise in patients with COPD (22).

We did not find that BLVR changed global inspiratory muscle strength. Nor were changes in these parameters correlated with change in exercise time, which suggests that this is not an important mechanism, at least in the short term. In this study an increase in Pdi,tw was correlated with reductions in FRC consistent with the known length–tension relationship of the diaphragm as previously demonstrated by our group and others (40, 41). Shortening muscles moves their force–frequency curve to the right so that low-frequency (i.e., single-stimulus) techniques are most sensitive to the change (42). Volitional maneuvers are known to be less sensitive to changes in lung volume (43), which may explain the apparent discrepancy in the results. We would argue that the increase in Pdi,tw is to an extent an epiphenomenon of resting lung volume change rather than a mechanism of improvement as such. Nevertheless, mechanical disadvantage and shortening of the inspiratory muscles will reduce their ability to overcome intrinsic positive end-expiratory pressure and the greater elastic load at higher lung volumes as the pressure–volume curve of the lung flattens. In the presence

of dynamic hyperinflation, the function of the respiratory muscle pump is limited by mechanical constraints on ventilation rather than by an inability of the respiratory muscles to sustain contraction as evidenced by the fact that diaphragm fatigue does not occur after exhaustive exercise in patients with COPD (44).

It is not clear by what mechanism $P_{E_{max}}$ improved because there was a reduction in TLC. The absence of a change in cough gastric pressure suggests that abdominal muscle strength was not significantly improved. Improvements in maximal expiratory mouth pressure might have arisen because of an improvement in the alignment of thoracic expiratory muscles, or because of better transmission of pressure.

The association between changes in FRC and Pdi,tw was similar in magnitude to those observed in other studies examining acute change either in a laboratory setting (40) or after surgical intervention (31, 32, 45, 46). In particular, the fact that a decrease in FRC was associated with an increase in Pdi,tw suggests that the optimal length for the diaphragm in patients with COPD lies below the FRC.

We chose to target the most affected lobe of lung in patients with heterogeneous emphysema because this approach appears to be most successful in LVRS (2). Selecting the most appropriate patients for BLVR remains problematic. It is clear that patients with the mildest disease are unlikely to benefit from the intervention whereas in patients with the most severe disease it may either be ineffective or hazardous, as it could further reduce the lung available for gas transfer and expose patients to the risk of pneumothorax (5, 7, 8). We found that improvement was greatest in those with the highest respiratory rates during baseline exercise and would therefore support the use of cardiopulmonary exercise testing as part of the selection criteria as well as pulmonary function. From a clinical perspective it is worth noting that patients whose exercise was wholly or partly limited by leg discomfort were less likely to benefit. This is consistent with the concept that interventions to improve exercise capacity by improving ventilation may not be effective if exercise is limited by leg fatigue (47, 48).

The targeting strategy may also be important. Snell and coworkers studied patients with upper lobe–predominant emphysema and aimed to produce bilateral upper lobe obstruction. This produced improvements in gas transfer but no evidence of atelectasis or significant improvements in lung volumes (7). By contrast, Yim and coworkers, using a predominantly unilateral approach guided by $\dot{V}/\dot{Q}$ scan as well as CT produced greater than 75% collapse in 4 of 20 lobes targeted (8), results more comparable to our own. It may be that lobar collapse is facilitated if there is some potential for expansion contralaterally. However, it must be noted that radiologic atelectasis was not a prerequisite for physiological benefit, and that the mechanisms of benefit are similar whether or not it occurs.

Finally, this study adds to the body of literature demonstrating that BLVR is a relatively safe technique, which produces significant benefit in some patients, particularly those with the most restricted ventilation. A further question remains as to the time course over which improvements may occur as well as their duration. Clarification of its role in the management of COPD will depend on the results of larger randomized controlled trials, which are now in progress.

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Bronchoscopic lung volume reduction: indications, effects and prospects

Nicholas S. Hopkinson

Purpose of review
Despite optimal pharmacological treatment, many patients with chronic obstructive pulmonary disease remain very disabled. Bronchoscopic lung volume reduction involves the insertion of valves into the airways supplying emphysematous areas of lung with the intention of causing atelectasis and thus improving operating lung volumes. Bronchoscopic techniques are less hazardous than lung volume reduction surgery.

Recent findings
Case series in the literature are reviewed. The presence of extensive pathological collateral ventilation, particularly in patients with homogeneous disease, means that atelectasis occurs relatively infrequently even with complete lobar occlusion. Benefit is greatest in the presence of atelectasis but does not occur only in this group of patients. Endobronchial valves have also been used to treat persistent air leaks in a number of clinical contexts.

Summary
A number of case series have been published which show promise and the results of a large multicentre randomized controlled study are anticipated in 2007. A number of other bronchoscopic treatments for emphysema are also under development, including airway bypass techniques and tissue glues.

Keywords
chronic obstructive pulmonary disease, devices, endobronchial

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Abbreviations

BLVR	bronchoscopic lung volume reduction
COPD	chronic obstructive pulmonary disease
EBV	endobronchial valve
FEV_1	forced expiratory volume in 1s
LVRS	lung volume reduction surgery

1070-5287

Introduction

Patients with advanced chronic obstructive pulmonary disease (COPD) continue to experience exertional breathlessness despite optimum medical therapy. In selected patients, lung volume reduction surgery (LVRS) has been shown to improve exercise capacity and quality of life [1–3]. LVRS, however, is not without risk. In particular, the National Emphysema Treatment Trial (NETT) found an excess mortality (16% at 30 days) in patients with the most severe disease. Even when high-risk patients were excluded, surgical volume reduction has been associated with significant morbidity and an early mortality rate of about 5% [1,2]. For this reason, there is a need for safer alternatives. Bronchoscopic lung volume reduction (BLVR) has the potential to become such an alternative. A number of other bronchoscopically delivered techniques for the treatment of emphysema will also be touched on briefly in this review.

BLVR involves placing a device to obstruct the airway(s) leading to the most hyperinflated, emphysematous parts of the lung. The rationale for this approach is that endobronchial obstruction should cause these areas to collapse and thus, by reducing hyperinflation, alleviate symptoms without recourse to surgery. The technique was first performed using airway blockers [4,5] and subsequently our group [6,7•] and others [8,9,10•,11,12] have described early experience with the use of purpose designed endobronchially placed valves. A one-way valve is preferred as it allows air to exit the targeted lobe during expiration facilitating atelectasis. This permits secretions to drain and most importantly prevents the occurrence of potentially life-threatening acute local hyperinflation which can occur when the occluding device acts as a one-way valve the wrong way, with breaths stacking up behind the occlusion.

Available devices

Two valves are currently being evaluated in clinical trials. The Spiration Implantable Intrabronchial Valve (IBV valve; Spiration Inc., Redmond, Washington, USA) (Fig. 1) is an umbrella-shaped device composed of a nitinol framework with struts covered by a flexible synthetic polymer cover. It is deployed from a catheter passed through the working channel of a bronchoscope. As the umbrella expands, the valve conforms to the shape of the bronchial wall with the umbrella permitting air to be exhaled but not inhaled. If the proximal central rod of

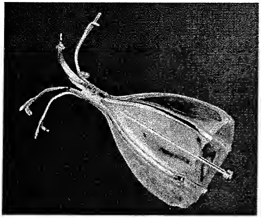

Figure 1 Spiration intrabronchial umbrella valve

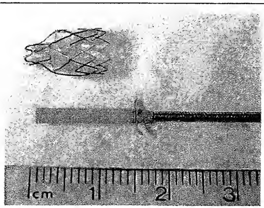

Figure 3 Emphasys third-generation 'Zephyr' endobronchial valve and delivery catheter capable of being deployed through the working channel of the bronchoscope

the valve is grasped the umbrella collapses allowing the valve to be readily removed. This valve is the subject of a multicentre controlled trial but to date there are no published data in patients.

More evidence is available regarding the efficacy of the endobronchial valves (EBVs) produced by Emphasys Medical (Redwood City, California, USA). The first two devices were nitinol stents of a fixed size with a proximal silicone seal and an internal silicone duckbill valve that prevents air from entering the target lung but allows air and mucus to exit (Fig. 2). Deployment of the first two versions of the valve required a wire exchange technique. A guidewire was passed into the selected orifice, the bronchoscope was removed and then the delivery catheter passed over the wire. The bronchoscope was reinserted so that the valve could be deployed under direct vision. Three sizes of valve were available.

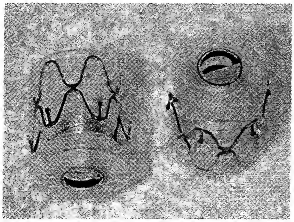

Figure 2 Emphasys second-generation endobronchial valve

The third and most recent version of the Emphasys EBV, the Zephyr valve, can now, like the Spiration IBV valve, be delivered from a catheter passed through the working channel of a bronchoscope (Fig. 3). Two sizes of valve are available, 4 or 5.5 mm. A sizing device is passed down the bronchoscope first to enable the operator to select the appropriate size of valve for the airway that is being occluded. When deployed, the device expands to occlude the airway lumen. This device offers less resistance to expiratory flow, which in theory should improve emptying of the target lobe. The Zephyr valve is intended to be easy to remove if necessary.

Results of case series in humans using the Emphasys endobronchial valve

Snell *et al.* [8] studied 10 patients suitable for conventional LVRS, with upper lobe predominant heterogeneous emphysema. They targeted both upper lobes, aiming to occlude all segmental bronchi. There were no major complications. None of the patients, however, had significant atelectasis on computed tomography scanning at 30-day follow up. There was a significant decrease in upper lobe blood flow assessed by ^{99m}Tc perfusion scanning and a significant improvement of gas transfer but without significant change in measures of airflow obstruction or lung volume. Of note, and contrary to other findings, subsequent bronchoscopic inspection revealed the valves to be venting in expiration in the majority of patients. It is probable that this was because of problems with the earliest valve design.

The other published case series have for the most part used the second-generation EBV, with some early

experience with the third-generation valve also reported. We described outcomes in 19 patients with heterogeneous emphysema, mean (SD) forced expiratory volume in 1 s (FEV_1) of 28.4% (11.9%) predicted, who had unilateral valve insertion [7•]. Initially, we inserted these valves under general anaesthetic [13]. Subsequently, some procedures were carried out with sedation only and some of these were staged, with valves being inserted on two separate occasions, 1–2 weeks apart. The final four patients received the third-generation valve.

At 4 weeks after the procedure, mean functional residual capacity had fallen significantly from 7.1 (1.5) to 6.6 (1.7) l and diffusing capacity risen from 3.3 (1.1) to 3.7 (1.2) mmol $min^{-1} kPa^{-1}$. Cycle endurance time at 80% of peak workload pre-procedure increased dramatically from 227 (129) to 315 (195) s. This was associated with an improvement in dynamic hyperinflation, with a reduction in end-expiratory lung volume at peak exercise from 7.6 (1.6) to 7.2 (1.7) l. Using stepwise logistic regression analysis, a model containing changes in transfer factor and resting inspiratory capacity explained 81% of the variation in change in exercise time. The same variables were retained if the five patients with radiological atelectasis were excluded from analysis, although the magnitude of improvement was less. In a subgroup of patients in whom invasive measurements were performed, improvement in exercise capacity was associated with a reduction in lung compliance and work of breathing assessed as isotime oesophageal pressure–time product. Two patients developed pneumothoraces, one requiring intercostal tube drainage.

Yim *et al.* [9] have described the results of predominantly unilateral valve insertion in 21 patients, targeting the most emphysematous segments using the second-generation valve. At 90 days follow up they observed significant increases in FEV_1 and vital capacity as well as 6 min walk distance, Medical Research Council (MRC) dyspnoea score and quality of life. Only four patients had over 75% collapse in the target lobe [9].

Venuta *et al.* [11] performed unilateral BLVR in 11 patients and staged bilateral procedures in two using second-generation valves. A severe group of patients were chosen, all requiring supplemental oxygen at rest prior to the procedure. Six complications occurred in three patients: two bilateral and one contralateral pneumothorax, one pneumonia, and two episodes of bronchospasm. Functional results at 1 and 3 months showed a significant improvement in FEV_1, residual volume, and 6 min walk test; 43% of the patients no longer required supplemental oxygen. The posttreatment MRC median dyspnoea score at 1 and 3 months was 2. Bronchoscopic follow up at 1 and 3 months showed that the valves were correctly in place with no granulation. The rate of radiological atelectasis is not reported.

de Oliviera [12] described the results of EBV insertion in 19 patients (eight bilateral) with heterogeneous emphysema, 12 receiving third-generation valves. A statistically significant improvement in 6 min walk distance was observed at 1 month but no significant difference in lung function parameters. There was transient radiological atelectasis in two patients but this did not persist. Two developed a pneumothorax, one of which required the removal of the valves, and in another patient the valves were removed because of respiratory dysfunction and bronchial hypersecretion. This group reported that granulation tissue occurred commonly with the second-generation valve but only infrequently (one out of 10 at 1 year follow up) in the third-generation valve.

The largest series to date describes 98 patients with COPD treated with the second-generation EBV in multiple centres. An average of four valves per patient were inserted. Exercise tolerance and lung function improved significantly with an acceptable safety profile at 90 days [10•]. The incidence of radiological atelectasis is unfortunately not reported. Three patients developed pneumothoraces requiring surgical intervention and four prolonged air leaks occurred. Pneumothoraces occurred exclusively in patients in which an entire lobe was targeted. One patient died having developed pneumonia in a targeted part of the lung. Patients with the most gas trapping at baseline (residual volume over 225% predicted) also tended to have the greatest improvement. There was a trend towards greater improvement in patients treated unilaterally rather than bilaterally and in those who had treatment targeting an entire lobe. This finding needs to be treated with caution as these were not a-priori categories; targeting strategy and patient selection criteria varied between sites and the two factors were not independent, because targeting was more likely to be lobar when a unilateral approach was adopted. It may also be that lobar collapse is facilitated if there is some potential for expansion contralaterally

Mechanisms for success or failure

Although atelectasis of emphysematous lung is the intended consequence of BLVR, pilot work has shown both that lobar collapse occurs relatively infrequently and that it is not necessary for clinically apparent benefit, suggesting that other physiological mechanisms must operate. It should be noted that this assessment can be technically difficult because the emphysematous destruction present makes accurate location of landmarks such as fissures problematic. The presence of collateral ventilation was first confirmed by Van Allen *et al.* [14], who observed that significant gas exchange and ventilation could occur distal to a complete bronchial

obstruction, implying that there must be connections between obstructed and unobstructed lung. The process of alveolar destruction that occurs in emphysema leads to a destruction of normal lung architecture, with incomplete interlobar fissures more common in emphysematous than in normal lungs [15]. Significant collateral ventilation through alveolar–lobar pores has also been observed at postmortem in these patients [16]. Recently, interlobar collaterals have been demonstrated in 15 out of 23 explanted lungs from patients with severe emphysema undergoing lung transplantation [17•]. Importantly, the presence of collaterals was associated with a homogeneous distribution of emphysema on computed tomography scan and this suggests that patients with heterogeneous disease may benefit more from valve treatments as is the case with LVRS. Intuitively, it seems likely that collateral ventilation will occur within a lobe more frequently than between lobes, which may explain the trend towards greater benefit when a lobar approach is taken [10•].

A key element in the ventilatory limitation of exercise in COPD is the development of dynamic hyperinflation, where expiratory flow limitation leads to a progressive increase in end expiratory lung volume during exercise and consequently restricts the tidal volume that can be achieved (reviewed in Calverley *et al.* [18•]). We have demonstrated that BLVR is associated with improved exercise capacity in the context of reductions in dynamic hyperinflation. This also occurred (though to a lesser extent) in patients who did not have radiological atelectasis. In patients with only a modest amount of collateral ventilation, valve insertion may still direct airflow into less affected areas of lung, reducing dynamic hyperinflation during exercise.

Gas transfer improves significantly following valve insertion, and we found that change in this parameter was highly correlated with improvement in exercise capacity. BLVR may allow the recruitment of previously 'compressed' alveolar units. BLVR may improve cardiac function by reducing intrathoracic pressure swings (as observed in our series), thus increasing pulmonary capillary volume, as has been observed following LVRS [19]. If the targeted area of lung is the most emphysematous, it would be expected to have the slowest time constants and might therefore have been contaminating the 'alveolar' part of the sample during the expiration when gas transfer was measured prior to the procedure. Excluding this area from ventilation would reduce inhomogeneity of gas mixing. This mechanism may more properly be thought of as a measurement error, although it does reflect emphysematous pathophysiology. Interestingly, improvements in gas transfer appear to be a consistent feature of BLVR whereas following LVRS, perhaps because the technique inevitably requires the removal of some relatively normal lung tissue, it has not improved in a number of studies [1,20], although this has not been a universal finding [21,22].

LVRS is known to improve inspiratory muscle function [22] and we found that the reduction in static lung volumes we observed following BLVR was also associated with an improvement in diaphragm function, assessed as twitch transdiaphragmatic pressure in response to anterolateral magnetic phrenic nerve stimulation [7•].

Collapse of a targeted lobe following BLVR may also be hindered by pleural adhesions and these may also, if collapse does occur, cause parenchymal tears and a risk of pneumothorax. Pneumothorax may also occur if the rapid expansion of a bulla in an adjacent lobe causes it to rupture, as observed in one case [10•] in which a right lower lobe bulla had ruptured following targeting of the right upper lobe which had led to lobar atelectasis. Some of the pneumothoraces observed are likely to have occurred *ex vacuo* rather than because of an air leak.

In our series, improvement in exercise capacity was greatest in those with the highest respiratory rates during their baseline exercise test. We also observed that patients whose exercise was wholly or partly limited by leg discomfort were less likely to benefit, which is consistent with the concept that interventions to improve exercise capacity by improving ventilation may not be effective if exercise is limited by leg fatigue [23,24].

Use of endobronchial valves to close persistent air leaks

A number of case reports have been published describing the successful treatment of persistent air leaks using EBVs in a range of contexts [25–30]. Examples of these include following lung resection for aspergilloma [28], after feeding tube malpositioning [26], following LVRS [30], in disseminated malignancy [27] and in empyema [29]. Theoretically it may be appropriate to remove the valve or valves subsequently, assuming that the hole in the pleura has healed, but since the valves appear to be well tolerated none of the groups have reported going on to do this.

Other bronchoscopic approaches to treat emphysema

The airway bypass technique involves inserting stents from cartilaginous airways into emphysematous lung, providing additional pathways for expiration. This should reduce gas trapping and by producing a low resistance pathway should have more effect in the presence of collateral ventilation rather than being hindered by it. Broncus Technologies Inc. (Mountain View, California) have developed a system in which stents are inserted under Doppler ultrasound guidance to ensure that blood

vessels are not punctured. Initial work [31] has shown this technique to be feasible, with studies in the lungs of patients with emphysema at surgery prior either to lobectomy or transplantation [31]. Pilot data are accumulating in patients, though none have yet been published. A multicentre randomized controlled trial is due to start by the end of 2006.

Another approach has been to find tissue engineering approaches that will produce lung volume reduction by causing scarring in target areas of the lung [32,33]. Only animal data are available at present and it remains unclear whether it will be possible to apply this technique to humans. It is possible that these substances could be used in conjunction with endobronchial devices in order to facilitate atelectasis. An obvious technical issue, given the presence of collateral pathways, is ensuring that the substance used is confined to the target area and does not spill into healthier areas of the lung. Short-acting agents that are suspended in a foam or biogel may address this.

Conclusion

Studies of BLVR that have so far been published have all been uncontrolled and unblinded, and as such, are open to potential bias from enthusiastic investigators and optimistic patients. They do provide encouraging, preliminary data about the safety and efficacy of these devices. The results of a multicentre randomized trial of BLVR using the EBV, the Endobronchial Valve for Emphysema Palliation Trial (VENT), are anticipated in 2007. Other trials are also underway which together will hopefully provide a definite indication of the future for these new technologies. It may prove to be the case that valve insertion will be the appropriate therapy when there is heterogeneous disease and a target lobe can be identified. In homogeneous disease, with intralobar collateral ventilation being more likely, the airway bypass approach may prove to be preferable. Alternatively, it may be that rather than relying on these categories, direct measurement of collateral ventilation [34] using mass spectroscopy will be a better approach.

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Computed tomography assessment of lung volume changes after bronchial valve treatment

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ABSTRACT: **The aim of the present study was to correlate clinical outcome measures following treatment with bronchial valves with regional lung volume. Computed tomography (CT) scan data from 57 subjects with severe emphysema were obtained from nine North American clinical trial sites. IBV® Valves (Spiration, Inc., Redmond, WA, USA) were placed to occlude segmental and subsegmental bronchi in right and left upper lobes using a flexible bronchoscope. Subjects completed a St George's Respiratory Questionnaire (SGRQ), pulmonary function test (PFT) and exercise capacity test. CT scans were analysed at baseline and at 1, 3 or 6 months after treatment to measure total and lobar lung density, volume and mass.**

Total lung volumes measured using CT were strongly correlated with PFT and did not change with treatment. However, the treated upper lobes significantly decreased in volume in 88% of the observations, by mean±SD 335±444 mL, or a decrease of 10.2% in the 6 month data. The untreated lobes had an 11.6% increase in volume. Changes in regional lung volume were associated with clinically meaningful improvements in SGRQ (-8.95±16.22), but not clinically meaningful PFT changes.

The significant health status improvements reported by subjects following bilateral bronchial valve treatment are associated with regional lung volume changes and interlobar shift measured using computed tomography.

KEYWORDS: **Computed tomography, emphysema, intrabronchial valve, lung volume reduction surgery**

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STATEMENT OF INTEREST
Statements of interest for H.O. Coxson, N.L. Müller, D.H. Dillard, C.L. Finger and S.C. Springmeyer, and for the study itself, can be found at www.erj.ersjournals.com/misc/statements.shtml

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Chronic obstructive pulmonary disease (COPD) is the most common form of primary pulmonary disability [1, 2] and an important cause of mortality when severe. As COPD becomes an end-stage disease, palliative surgical procedures, such as bullectomy for giant bullae, lung volume reduction surgery (LVRS) and lung transplantation, are the only potential treatments remaining.

The National Emphysema Treatment Trial (NETT) and some other smaller studies have shown that, in a selected population of patients with heterogeneous distribution of emphysema and upper-lobe predominance, LVRS can improve patient quality of life, as well as respiratory function, exercise capacity and survival [3–8]. However, surgery in these already high-risk patients has a significant morbidity (20–30%) and a considerable operative mortality (7.9%) within 90 days of the procedure [9].

Therefore, minimally invasive techniques have been proposed as a method to reduce lung volume in these patients without undergoing open thoracotomy [10–15]. One of these new treatments is a one-way valve, which is placed in the segmental bronchi of the most diseased lobes, generally the upper lobes, to prevent air from entering these portions of the lung during normal inspiration while still allowing air to exit. The original hypothesis for this procedure was that the delivery of gas to the treated lobes would be lower than the absorption of gas in these regions resulting in lobar atelectasis, and a reduction of total volume in the diseased lung [11, 12, 15]. This overall reduction in lung volume would result in functional and clinical improvements, similar to those seen with LVRS, but without the invasive surgical procedure. However, several studies have found that the majority of subjects with clinical improvement did not have atelectasis and total lung volume

reduction, so other mechanisms of action have been considered and investigated [15, 16].

The purpose of the present study was to correlate clinical outcome measures with objective and subjective quantification of lobar lung volumes in patients with severe upper-lobe predominant emphysema treated with one-way bronchial valves. The current hypothesis was that as bronchial valves block distal airflow, the treated lobes would have a decrease in volume that could not be measured using physiological lung pulmonary function methods.

MATERIALS AND METHODS

Computed tomography (CT) scan data from 57 subjects with severe emphysema were obtained from nine North American clinical trial sites. All studies were approved by the appropriate institutional review board or ethics committee and all subjects gave informed consent to receive treatment with the IBV® Valve System (Spiration, Inc., Redmond, WA, USA) and have their clinical information collected.

These 57 subjects are a subset of 98 subjects from North American pilot studies (clinicaltrials.gov identifier NCT00145548) in which CT scan data could be obtained. All 98 subjects received an initial CT scan to determine whether they met the selection criteria for severe, upper-lobe predominant emphysema. The first 34 subjects enrolled in the trial received a second CT scan after 1 month to plan for a second bronchoscopic procedure, which produced 34 paired baseline and 1-month scans for analysis. When the quantitative CT study was initiated, subjects that had not yet reached their 6-month follow-up received another CT scan; this provided 16 paired scans for baseline and 6-month analyses. Finally, subjects enrolled after the initiation of the quantitative CT scan also received a CT scan at 3 months post-valve placement to provide a total of 34 paired baseline and 3-month scans. Some subjects received CT scans at more than one time point, and accordingly, the number of paired data sets exceeds the number of patients.

The inclusion/exclusion criteria of subjects have been previously reported [15]. Briefly, subjects were included if they had severe airflow limitation (forced expiratory volume in one second (FEV1) $\leqslant$45% predicted), hyperinflation (total lung capacity (TLC) $\geqslant$100% pred and residual volume (RV) $\geqslant$150% pred), a 6-min walk test (6MWT) distance of >140 m and severe emphysema that was determined to be upper-lobe predominant using the radiological comparison method that gave predictive results in the NETT [17]. Subjects were excluded if they had the high-risk criteria defined by NETT, signs of active infection or bronchospasm, were deemed to have lower-lobe predominant, diffuse, or superior segment of the lower lobe predominant using the radiological comparison method, or were listed for LVRS or lung transplantation.

Bronchial valve placement

The bronchoscopic procedure and valve placement has been previously described [15]. Briefly, after anaesthesia and endotracheal intubation, the sizes of the target airways were determined using a calibrated balloon catheter. Valves of the appropriate size were placed in both upper lobes using previously described techniques [15].

Clinical data

All subjects received a pulmonary function test (PFT) including spirometry (FEV1 and forced vital capacity (FVC)), plethysmography for static lung volumes (TLC, RV and functional residual capacity) as well as the diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) using the single-breath carbon monoxide method. These measures were made at baseline (n=57), 1 month (n=52), 3 months (n=53) and 6 months (n=45) after treatment with bronchial valves. Disease-specific health-related quality of life (HRQL) was measured using the St George's Respiratory Questionnaire (SGRQ) at the described time points. The SGRQ was completed during clinical stability with a four-point or greater change indicating a clinically meaningful improvement and defined as a responder.

Radiological imaging

CT scans were obtained using a high-resolution CT protocol (1 or 1.25 mm slice thickness, 10 mm gap; n=4), a multislice CT protocol (1 mm slice thickness, contiguous images; n=13) or thick slice protocol (5 mm slice thickness, contiguous images; n=40).

Data analysis

All CT scans were analysed at the University of British Columbia (Vancouver, BC, Canada) using both a qualitative and a quantitative procedure. For the qualitative analysis, two independent readers (F.V. Nasute Fauerbach and N.L. Müller) reviewed the CT scans. For the baseline CT scans the following parameters were considered: distribution of emphysema (upper-lobe or nonupper-lobe predominant), predominant type of emphysema (centrilobular, panacinar or paraseptal); and the extent of emphysema (marked/grade 3: 50–75%; and severe/grade 4: >75%). This allowed comparison with the local site assessments for the inclusion criteria of severe, upper-lobe predominant emphysema. In the follow-up CT scans the following were reported: presence of volume loss distal to the endobronchial valve and its grade if present (no volume loss, linear atelectasis, mild atelectasis: volume loss equivalent to less than one segment, moderate atelectasis: volume loss was equivalent to one or more segments; or complete atelectasis: when the whole lobe was affected).

The quantitative analysis was performed by two different readers (C. Storness-Bliss and S. Cogswell) using custom software (EmphylxJ, Vancouver, BC, Canada) as previously reported [18, 19]. Briefly, the lung parenchyma was segmented from the chest wall and large central blood vessels in all CT images using a modified border-tracing algorithm with a prior position-knowledge algorithm. Total lung volume was calculated by summation of the segmented pixel area in each slice and multiplying by the slice thickness. Lobar volume was calculated by manually tracing the fissures and summation of the pixels as above. Three cases were analysed by both observers to check for interobserver variation in the fissure-tracing technique. The mean CT attenuation measured in HU of the lobe and total lung were calculated and converted to a measure of density in g·mL^{-1} by adding 1,000 to the HU number and dividing by 1,000 [20, 21]. The mean density of the lung was then multiplied by the lung volume to estimate lung mass.

Statistical analysis

The difference between contiguous variables was tested using a paired t-test. Correlation estimates were calculated using

TABLE 1 Clinical outcome measures over time: before and after treatment and the difference between baseline and time after treatment

	Baseline	1 month	3 months	6 months
FEV_1 L	0.84±0.23	0.82±0.22	0.80±0.22	0.79±0.23
Difference L		-0.03±0.14	-0.03±0.17	-0.04±0.16*
Subjects n	57	55	54	45
FVC L	2.76±0.84	2.75±0.83	2.81±0.74	2.59±0.73
Difference L		-0.03±0.48	0.12±0.46	-0.11±0.60*
Subjects n	57	55	54	45
TLC L	7.78±1.40	7.65±1.41	7.74±1.49	7.64±1.51
Difference L		-0.11±0.68	0.03±0.73	0.12±0.63
Subjects n	56	55	54	45
RV L	4.90±1.04	4.90±1.05	5.10±1.15	4.98±1.26
Difference L		0.03±0.87	0.19±0.93	0.02±0.94
Subjects n	56	55	54	45
$D_{L,CO}$ mL·min^{-1}	9.50±3.13	9.87±3.26	8.97±3.06	9.10±2.76
Difference mL·min^{-1}		0.09±2.11	-0.49±2.17	-0.29±1.99
Subjects n	56	54	54	45
6MWT m	336±85	345±90	349±85	348±97
Difference m		4±56	9±57	12±65
Subjects n	57	54	54	45
SGRQ	58.2±12.6	52.7±13.6	54.5±18.0	50.0±19.1
Difference		-5.49±13.60**	-4.28±15.61*	-8.85±16.22#
n	56	55	54	45

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-min walk test; SGRQ: St George's Respiratory Questionnaire. #: $p<0.0001$; *: $p<0.05$; **: $p<0.01$.

Spearman's method, unless otherwise specified. A CT responder was defined as any subject that had a decrease in the volume of the upper lobe and an increase in the nonupper lobe volume of >10%. A change in SGRQ of minus four or more points was considered a clinical responder. The association of responders with lobar volume changes and quality of life was tested using a Chi-squared test. A p-value of <0.05 was considered significant.

RESULTS

The clinical outcome (without CT analysis) of the initial 30 subjects in these studies has been previously reported [15]. The present group of 57 subjects with paired CT scans is an extension of the same protocols and is the first time that this data has been reported. Briefly, 346 implanted valves, a mean±SD of 6.06±1.96 per subject, were placed at the initial procedure. Most (84%) valves were placed by the catheter technique and 99.7% of the targeted upper lobe airways were successfully treated. Nearly all (54 (95%) out of 57) subjects had their bilateral upper lobes treated; three subjects received unilateral treatment because of pre-existing disease in one upper lobe, such as volume loss from a prior pneumonia. Most (76%) of the valves were placed in segmental bronchi and the remainder in subsegmental bronchi.

TABLE 2 Subjects with moderate or complete lobar atelectasis observed by computed tomography scan over time

Case number	Baseline	1 month	3 months	6 months
1	0	L-3	ND	ND
2	0	R-3	ND	ND
3	0	R-4	ND	ND
4	0	L-2	ND	L-3
5	0	R-3	R-3, L-3	ND
6	R-2	R-2, L-3	ND	ND
7	0	R-2, L-3	R-2, L-3	ND
8	0	ND	R-3, L-2	ND
9	0	R-4	ND	R-4
10	0	ND	R-4	ND
11	0	R-3	R-2	ND
12	0	R-2, L-3	ND	R-2, L-3

L: left; R: right side; 0: none; 1: linear; 2: mild; 3: moderate; 4: complete lobe; ND: scan not done.

There were no deaths in the current group of 57 subjects within 90 days of the procedure. The most frequent adverse events occurring within a day of the procedure were pneumothorax in four and bronchospasm in two subjects. One pneumothorax resolved without tube thoracostomy and the bronchospasm episodes were transient. Within a 30-day period there were 10 subjects with a COPD exacerbation with an additional 10 in a 90-day period. There were six subjects with episodes of bronchitis within 30 days and two more within 90 days. Other than episodes of dyspnoea, of which there were three within 30 days and two within 90 days, no respiratory complications occurred in >2 subjects in the designated time periods.

Pulmonary function, exercise and HRQL outcomes before and after treatment are shown in table 1 and are similar to those previously reported [15]. There was no significant improvement in FEV_1, FVC or $D_{L,CO}$, no significant decrease in TLC or RV, and a trend for improvement in the 6MWT distance (12 m (3.6%); p>0.10). The significant and clinically meaningful changes were improvement in HRQL as measured by SGRQ following the procedure (p<0.0001 for mean and mean change at 6 months).

The qualitative CT data showed high agreement regarding selection for severe upper-lobe predominant emphysema between the central reviewers and the clinical sites. There was clinical site and reviewer agreement regarding upper-lobe predominance in 54 (93%) out of 57 patients, while the remaining three disagreements were between upper-lobe predominance and diffuse disease. In two out of those three cases, the clinical site and only one of the two reviewers were in agreement. All findings were grade 3 or 4 severity (except two that were grade 2) and all but two findings were centrilobular emphysema; with one each being panacinar and paraseptal.

On follow-up, moderate or complete lobar atelectasis was observed in 12 (21%) out of 57 subjects at some point in the 6 months following valve implantation (table 2). There was no

TABLE 3 Quantitative computed tomography measurements at baseline and after treatment

	Baseline	1 month	3 months	6 months
Subjects n	57	34	34	16
Total lung				
Volume mL	6840 ± 1375	6737 ± 1383	6852 ± 1456	6429 ± 1605
Difference mL		54 ± 495	45 ± 347	39 ± 305
% change		-0.6 ± 7.8	0.9 ± 5.4	0.6 ± 5.3
Upper lobe				
Volume mL	3419 ± 872	3058 ± 845#	3165 ± 976#	3025 ± 1312***
Difference mL		328 ± 511#	318 ± 427#	335 ± 444***
% change		9.3 ± 14.1	9.5 ± 12.2	10.2 ± 12.7
Nonupper lobe				
Volume mL	3421 ± 867	3679 ± 869#	3687 ± 982#	3404 ± 1025#
Difference mL		274 ± 419#	274 ± 334#	374 ± 387#
% change		9.2 ± 13.9	8.4 ± 10.2	11.6 ± 11.6
Total lung				
Mass g	728 ± 183	714 ± 165	715 ± 181	680 ± 195
Difference g		2 ± 126	15 ± 139	-62 ± 108
% change		1.2 ± 15.3	-0.6 ± 16.6	-7.3 ± 13.0
Upper lobe				
Mass g	301 ± 90	259 ± 75**	266 ± 111***	238 ± 99***
Difference g		36 ± 67**	37 ± 72***	71 ± 63***
% change		10.5 ± 19.3	12.3 ± 19.5	22.6 ± 15.9
Nonupper lobe				
Mass g	427 ± 111	455 ± 105	449 ± 86	442 ± 113
Difference g		37 ± 75*	22 ± 96	9 ± 71
% change		10.2 ± 16.8	8.0 ± 17.5	3.0 ± 15.0
Total lung				
Density g·mL⁻¹	0.108 ± 0.026	0.107 ± 0.020	0.105 ± 0.019	0.107 ± 0.021
Difference g·mL⁻¹		0.000 ± 0.026	0.001 ± 0.020	0.012 ± 0.025
% change		2.8 ± 19.2	0.5 ± 17.2	7.2 ± 16.0
Upper lobe				
Density g·mL⁻¹	0.090 ± 0.024	0.087 ± 0.020	0.084 ± 0.022	0.080 ± 0.022
Difference g·mL⁻¹		-0.003 ± 0.028	0.003 ± 0.019	0.016 ± 0.028*
% change		1.2 ± 27.3	-1.9 ± 22.5	12.1 ± 22.4
Nonupper lobe				
Density g·mL⁻¹	0.129 ± 0.037	0.126 ± 0.023	0.128 ± 0.035	0.136 ± 0.040
Difference g·mL⁻¹		-0.002 ± 0.037	-0.002 ± 0.028	-0.013 ± 0.034
% change		1.8 ± 16.1	0.0 ± 16.2	7.3 ± 12.8

Data are presented as mean ± SD, unless otherwise stated. #: $p<0.0001$. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

atelectasis observed at any time point in 24 (42%) subjects and a linear or mild degree of atelectasis was present in 21 (37%) subjects. In addition, serial data showed that in six subjects with three scans, the degree of atelectasis decreased over time in one, increased in two and was stable in the other three subjects (table 2).

The quantitative CT measurements show that there was no change in the total lung volume, total lung mass or total lung density at 1, 3, or 6 months (table 3). However, there was

TABLE 4 Changes (Δ) in health-related quality of life, quantitative computed tomography, pulmonary function test and 6-min walk test (6MWT) results

Quantity 1	Quantity 2	Spearman's correlation	p-value
ΔSGRQ	Δ6MWT	-0.2436	0.1298
ΔSGRQ	ΔFVC	0.2417	0.1329
ΔSGRQ	ΔUpper lobe	0.1659	0.305
ΔSGRQ	ΔNonupper lobe	0.3809	0.0159
ΔSGRQ	ΔFEV1	-0.2245	0.1637
Δ6MWT	ΔFVC	0.4783	0.0018
Δ6MWT	ΔUpper lobe	-0.3316	0.0366
Δ6MWT	ΔNonupper lobe	0.2991	0.0608
Δ6MWT	ΔFEV1	0.2734	0.0878
ΔFVC	ΔUpper lobe	-0.3105	0.0512
ΔFVC	ΔNonupper lobe	0.3049	0.0557
ΔUpper lobe	ΔNonupper lobe	-0.473	0.0023
ΔUpper lobe	ΔFEV1	-0.449	0.0037
ΔNonupper lobe	ΔFEV1	0.3709	0.0185

SGRQ: St George's Respiratory Questionnaire; FVC: forced vital capacity; FEV1: forced expiratory volume in one second. Percentage changes were used for the quantitative computed tomography measures, and absolute change for the other measures in these analyses.

significant decreases at all time points in the treated upper lobe volume and mass and significant increases in the untreated nonupper lobes volumes. The average change in lobar volumes was ~300 mL, or 10%. The mean ± SD interobserver variation (range) in lobar volume was 2 ± 2% (0–5%) or 35 ± 31 mL (4–80 mL).

There was a strong correlation between the functional measurement of TLC by plethysmography and the CT

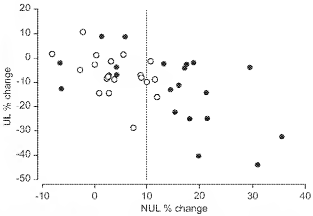

FIGURE 1. Scatter plot of percentage change in upper lobe (UL) volume change compared with nonupper lobe (NUL) volume change. ●: St George's Respiratory Questionnaire (SGRQ) responders; ○: SGRQ nonresponders, with a responder defined as a four-point or greater change; ····: threshold for a NUL response at 10%.

TABLE 5 St George's Respiratory Questionnaire (SGRQ) and computed tomography (CT) volume comparisons using all 40 subjects with 3- or 6-month paired CT data

	CT responder	CT nonresponder
SGRQ responder	14 (35)	7 (18)
SGRQ nonresponder	4 (10)	15 (38)

Data are presented as n (%). Correlation is significant at p<0.01 using Chi squared testing with continuity correction.

measurement of total lung volume. There were 56 paired samples obtained from baseline studies (r^2=0.77) and 138 total samples (r^2=0.79).

Correlations between 6MWT and PFT changes, HRQL changes, and changes in upper lobe and nonupper lobe volumes are shown in table 4. These indicate the correlation with improved SGRQ was a nonupper lobe volume increase. The PFT and 6MWT changes did not correlate with improved HRQL. There are correlations between some 6MWT and PFT measures and improvement in FEV_1 is correlated with a greater upper lobe volume decrease, but not with HRQL. Figure 1 shows the upper lobe and nonupper lobe changes which indicate that a ≥10% nonupper lobe volume could define a threshold for a CT response. Therefore, a subject with 10% increase in nonupper lobe volume and any decrease of upper lobe volume was defined as a CT responder. Using results from all 40 subjects with 3- or 6-month data (using 3-month if there was no 6-month data), these CT responders were compared with subjects with a greater than four-point change in SGRQ (table 5). There was a highly significant correlation between subjects that had an interlobar volume shift and HRQL (p<0.01).

DISCUSSION

The present study shows that the minimally invasive procedure of IBV® Valve (Spiration, Inc.) placement in the upper lobe bronchial segments decreases the end-inspiratory volume of the (more diseased) upper lobes and increases the volume of the untreated (less diseased) lobes, without producing an overall lung volume reduction. Furthermore, these lobar volume changes are significantly associated with clinically meaningful improvements in HRQL in subjects with severe upper-lobe predominant emphysema.

Until recently, LVRS or lung transplantation have been the only options for palliative treatment of end-stage emphysema. The NETT demonstrated that LVRS improves survival, HRQL and exercise capacity for as much as 6 yrs [3]. However, due to the significant morbidity and mortality associated with LVRS, many investigators have searched for a procedure to reduce lung volume without subjecting the patients to major surgery. Therefore, minimally invasive procedures that allow the treatment of severely diseased patients is a very active area of research [15, 22–24].

Most minimally invasive procedures started with the hypothesis that lung volume reduction *via* atelectasis would be the major mechanism for improvement. The present study shows that, according to CT assessment, atelectasis is infrequent, can be delayed in onset, and is often transient. This finding has also been reported in studies using other bronchial valves [25], raising the question about the original hypothesis that bronchial valves result in reduction of total lung volume [15, 23].

In the present study, quantitative CT was used to measure the changes in lobar lung volume due to bronchial valve placement. These data show that, while total lung volume, as measured by

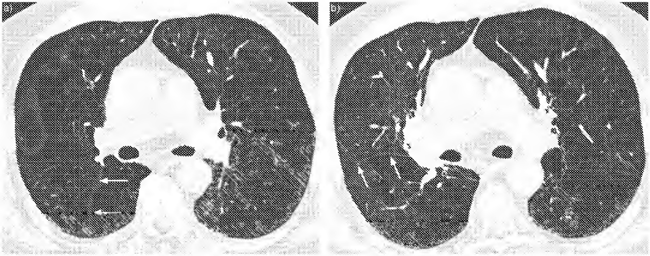

FIGURE 2. a) A computed tomography (CT) scan taken at baseline before the IBV® Valve (Spiration Inc., Redmond, WA, USA) treatment, and b) a matched CT scan acquired 6 months following treatment. Notice the shift in the major fissure (white arrow) in the right lung which was associated with a 1,555 mL decrease in upper lobe volume and a 1,200 mL increase in nonupper lobe volume.

CT and many other parameters such as TLC and FEV1, does not change, there is a significant decrease in the volume of the upper lobes. Since there is a compensatory change in the volume of the nonupper lobes, this change cannot be assessed using global measures and this probably explains why changes in pulmonary function cannot be assessed. An example of this change in lobar volume is illustrated in figure 2, where the major fissure in the right lung is clearly shifted anteriorly following valve placement corresponding to a 1,555 mL decrease in upper lobe volume and a 1,200 mL increase in nonupper lobe volume. This change in the treated lobe lung volume is similar to that reported in a small group of subjects at 7 and 30 days [26]. A significant volume change was documented in the present study 6 months following valve implantation, along with a decrease in upper lobe mass, suggesting less ventilation and perfusion to the treated lobes. Furthermore, an interlobar volume shift to the nontreated lobes was reported, which was associated with an improvement in the quality of life in the valve recipients. This improved HRQL is greatest on the impact component of the SGRQ, which measures factors such as being able to do household chores, talking without dyspnoea and feeling in control of their respiratory disease. The exact physiological mechanisms for improved HRQL is not apparent from these data, but the shift of volume and mass away from the treated lobes suggests the mechanism is related to more ventilation and perfusion to the untreated and less-diseased nonupper lobes.

The present authors propose that a lack of decrease in the upper lobe volume of all subjects could be due to a higher degree of collateral ventilation. Collateral ventilation has been shown to be an important method of gas movement in many subjects [27]. Collateral ventilation is slower than bronchial ventilation, so a modest degree of collateral ventilation may prevent complete atelectasis of the treated lobe but not prevent breath-by-breath changes in the ventilation of lobes, as these quantitative CT data indicate.

The current study has some limitations. The CT technique was not initially standardised between institutions, which resulted in different scanning techniques being used. However, this was a lung volume study, which is different from the lung densitometry studies that are commonly reported in the emphysema literature and are very reliant on CT protocol [19, 28]. In the current study, the interlobar fissure was identifiable in all of the CT scans; therefore, the present authors are confident that this limitation was overcome and the changes in lobar volume were quantified. A second limitation of the CT protocol was that there was no standardisation of inspiration during the CT scan. However, all of these subjects had very severe emphysema and, since they were breathing at or near TLC continuously and there was no change in the physiological TLC or CT measured total lung volume, it is likely that size of breath the subjects took during the CT scans were comparable and that the measured changes in lobar volume are reliable. In addition, not all of the CT scans used continuous acquisition and, therefore, contained gaps between the sections. However, it is well established from pathological studies that this type of volume sampling provides a reliable and unbiased estimate of volume, so the present authors are confident that the measurements taken reflect the volume of the total lung and individual lobes [29, 30]. Another limitation of the current study is that the fissures were manually traced by an observer. Furthermore, some of the CT scans were obtained using thick slices and some of the fissures were probably incomplete (data not available), which will produce some variation in the measurement of lobar volume. However, the interobserver variation due to manual tracing was measured to be $\leqslant 5\%$ (80 mL), which is well within the standard deviation of the measured lobar volume and, therefore, not likely to affect the results significantly. Finally, the present study had a relatively short-term follow-up with CT compared with the 6 yr follow-up now reported in studies for LVRS. The IBV® Valve (Spiration, Inc.) has been shown to have durable HRQL effects for 12 months [31]. These studies show that, similar to LVRS in the early stages, there is a change in some measure of lung volume and an improvement in quality of life suggesting that this technique may provide long-term benefits.

In conclusion, the current study shows that the implantation of bronchial valves results in changes in regional lung volumes that are associated with an improvement of patient quality of life. The present authors propose that the most common mechanism of action of bilateral bronchial valve treatment in severe upper-lobe predominant emphysema is not total lung volume reduction but a redirection, an inter-lobar shift, of inspired air to less diseased lung tissue.

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VENT PIVOTAL TRIAL
CLINICAL STUDY REPORT

Title:	**Endobronchial Valve for Emphysema PalliatioN Trial**
Short Title:	**VENT Pivotal Trial**
Protocol Number:	**Emphasys Protocol 630 – 0001 – J**
IDE Number:	**G020230**
Product:	**Emphasys Zephyr Endobronchial Valve**
Short Product Name	**Zephyr EBV**
Sponsor:	**Emphasys Medical, Inc.**
Initial Enrollment:	**December 22, 2004**
Final Enrollment:	**April 27, 2006**
Principal Investigator:	**Frank Sciurba, MD Associate Professor of Medicine Director, Emphysema Research Center Division of Pulmonary and Critical Care Medicine University of Pittsburgh Medical Center 3471 5th Ave., Suite 1117 Pittsburgh, PA 15213 Tel: (412) 648-6494 email: sciurbafc@MSX.UPMC.EDU**
Sponsor Signatory:	**Rich Ferrick, Vice President, RAQA Emphasys Medical, Inc. 700 Chesapeake Drive Redwood City, CA 94063 Tel: (650) 364-0400, x108 email: rferrick@emphasysmedical.com**
Good Clinical Practices:	**This study was conducted in compliance with applicable FDA requirements for Investigational Device Exemptions**
Date of Report:	**August 28, 2008**

CLINICAL STUDY REPORT SYNOPSIS

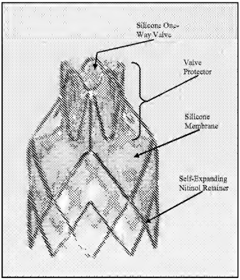
INTRODUCTION:

The Endobronchial Valve for Emphysema PalliatioN Trial ("VENT Pivotal Trial") was a randomized controlled clinical trial to assess the safety and effectiveness of using the Zephyr EBV device in the palliation of subjects with severe heterogeneous emphysema. Three hundred and twenty one (321) subjects were enrolled, assessed, optimized via medication and pulmonary rehabilitation, and then randomized to either a medical Control Group or Zephyr EBV Treatment. Follow-up included assessment of pulmonary parameters such as FEV_1 and the 6 minute walk test ("6MWT"), other secondary outcome measures, the occurrence of Major Complications and other adverse events.

INVESTIGATIONAL DEVICES (FROM SECTION 3.0):

The investigational devices comprised a system to implant one-way valves in the airways, which included the following components:

- Emphasys Zephyr Endobronchial Valve (Zephyr EBV)
- Zephyr Endobronchial Delivery Catheter (Zephyr EDC)
- Zephyr Endobronchial Loader System (Zephyr ELS).



STUDY DESIGN (FROM SECTION 4.0):

The primary objective of the VENT Pivotal Trial was to assess the safety and effectiveness of the Emphasys Endobronchial Valve (Zephyr EBV) and procedure compared to optimal medical management in subjects with heterogeneous emphysema.

The VENT Pivotal Trial was a randomized, controlled, multi-center trial enrolling 321 subjects with severe heterogeneous emphysema. The study design—including the use of a control group, the target patient population, the primary and secondary outcome measures and length of subject follow-up—was substantially based on the recommendations of the FDA Advisory Panel Meeting held in February, 2003.

After granting informed consent and meeting enrollment criteria, study subjects all underwent history and physical examination, evaluation of pulmonary function and morphology including high resolution CT scanning (HRCT), followed by a program of optimal medical management and aggressive pulmonary rehabilitation. Upon successful completion of this program subjects were randomized to either the Control or Zephyr EBV Treatment.

Zephyr EBV Subjects underwent bronchoscopic Zephyr EBV implantation under the provisions of the protocol which limited treatment to only one lobe (upper or lower lobe on one side). Complete exclusion of the target lobe was attempted by placing one or more Zephyr EBVs in lobar, segmental and / or subsegmental airways. Post-procedure, Zephyr EBV Subjects remained in the hospital and were observed for complications for at least 1 day.

Subsequent follow-up for all subjects consisted of assessment of a variety of relevant pulmonary and general outcome measures as evaluated by specific spirometry, body plethysmography, diffusing capacity, QoL instruments and exercise tests. Follow-up and outcome assessments were scheduled for 2 – 3 days, 1 week, 1, 3, and 6 months, and 1 year.

The <u>primary effectiveness outcomes</u> were the percent changes in both FEV_1 and 6MWT in Zephyr EBV Subjects compared to Control Subjects determined at the 6 month follow-up visit; superiority had to be demonstrated in both measures to meet the outcome.

The <u>primary safety outcome</u> for the VENT Pivotal Trial was the proportion of subjects in each group with one or more events specified as components of the Major Complications Composite (MCC) through 6 months of follow-up. The components of the MCC were death (all-cause), empyema, massive hemoptysis resulting in respiratory failure or blood loss > 300 cc in ≤ 24 hours, pneumonia distal to the implanted valves, pneumothorax or prolonged air leak > 7 days, and respiratory failure on mechanical ventilation > 24 hours.

<u>STUDY ACCOUNTABILITY (FROM SECTION 5.0):</u>

Thirty one (31) Investigators at 31 Investigative Sites enrolled a total of 321 study subjects between December 22, 2004 and April 27, 2006.

For 101 Control Subjects through 6 months of follow-up, 8 subjects withdrew informed consent and none had died, leaving 93 subjects alive and potentially evaluable at 6 months, of whom 79 (84.9%) had an evaluable visit. For 220 Zephyr EBV Subjects through 6 months of follow-up, 9 subjects withdrew informed consent and 6 died, leaving 205 subjects alive and evaluable at 6 months, of whom 193 (94.1%) had an evaluable visit for 6 months.

There were no unaccounted devices/components at the end of the clinical study.

All 321 subjects (100.0%) had a baseline HRCT evaluable for inclusion criteria. Of these 321 subjects originally enrolled, 280 were still in study follow-up as of the 6 month follow-up visit (Imaging Evaluable Subjects). Of these 280 Imaging Evaluable Subjects, 273 (97.5%) had a 6-month HRCT accepted by the Core Radiology Laboratory for protocol-specified imaging. HRCTs evaluable for fissure integrity at baseline were obtained in 93.8% of subjects, and paired baseline and 6-month images evaluable for lobar volume reduction at 6 months were obtained in 95.7% of subjects. HRCTs evaluable for valve position and lobar exclusion at 6 months were obtained in 98.5% of the Zephyr EBV Subjects.

BASELINE SUBJECT CHARACTERISTICS (FROM SECTION 6.0):

The mean age of the 101 Control Subjects was 64.9 years and of the 220 Zephyr EBV Subjects the mean age was 65.3 years ($p = 0.56$). Weight and height were comparable; the mean BMI for Control Subjects was 24.8 kg/m^2 and for Zephyr EBV Subjects was 25.1 kg/m^2 ($p = 0.51$). Mean blood pressures for the two groups were nearly identical ($p = 0.67$ systolic and $p = 0.49$ for diastolic). Males predominated in the Zephyr EBV Subject group (60.4%) compared to the Control Subject group (48.5%), the difference was nearly significant ($p = 0.052$). Both groups were almost entirely Caucasian.

All subjects (100%) in both the Control Subject and Zephyr EBV Subject groups were taking bronchodilators, steroids and mucolytics upon study entry.

Key medical factors were similar between the Control Subjects and Zephyr EBV Subjects. Diabetes was present in 5.0% of Control Subjects and 7.7% of Zephyr EBV Subjects ($p = 0.48$). An abnormal ECG upon study enrollment was found in 42.6% of Control Subjects and 45.9% of Zephyr EBV Subjects ($p = 0.63$). All but three study subjects had a history of smoking (98.0% Control Subjects, 99.6% Zephyr EBV Subjects, $p = 0.23$), with similar years of smoking (36.1 and 37.7 years respectively, $p = 0.17$) and pack-years (61.7 and 63.3 pack-years respectively, $p = 0.64$).

Supplemental oxygen use was also not different between the two study groups, with 41.7% of Control Subjects and 43.9% of Zephyr EBV Subjects using oxygen ($p = 0.77$). Hours of oxygen use daily were similar at rest (7.1 and 7.7 hours respectively, $p = 0.49$), during exertion (2.7 and 2.2 hours respectively, $p = 0.28$) and while sleeping (6.8 and 6.7 hours respectively, $p = 0.79$). Oxygen flow rates were also equivalent at rest (1.5 and 1.4 liters / min, $p = 0.58$), during exertion (2.6 and 2.4 liters / min, $p = 0.22$) and while sleeping (2.0 and 1.9 liters / min, $p = 0.21$).

There were no significant differences in any baseline lung function parameters between the Control Subjects and the Zephyr EBV Subjects. FEV_1 and FEV_1 % Predicted were respectively 0.84 liters and 30% in Control Subjects and 0.87 liters and 30% in Zephyr EBV Subjects. FVC and FVC % Predicted were respectively 2.62 liters and 70% in Control Subjects and 2.71 liters and 70% in Zephyr EBV Subjects. DL_{CO} and DL_{CO} % Predicted were respectively 10.15 mL CO / min / mmHg and 36% in Control Subjects and 9.52 mL CO / min / mmHg and 33% in Zephyr EBV Subjects. RV and RV % Predicted were respectively 4.63 liters and 212% in Control Subjects and 4.79 liters and 216% in Zephyr EBV Subjects.

Baseline arterial blood gas values were largely similar between the Control Subjects and the Zephyr EBV Subjects. The partial pressure of oxygen (68.4 and 69.1 mmHg, $p = 0.51$) and the oxygen saturation (93% and 93%, $p = 0.71$) were not different, nor was the pH (7.42 and 7.43, $p = 0.48$). However, the Control Subjects had a slightly higher mean partial pressure of carbon dioxide (41.6 compared with 40.5 mmHg, $p = 0.044$) and a borderline higher bicarbonate (26.9 compared with 26.3 mEq / liter, $p = 0.09$).

Baseline BODE Index scores were quite similar between Control Subjects and Zephyr EBV Subjects, 4.2 and 4.4 respectively ($p = 0.2551$). Baseline SGRQ scores were quite similar between Control Subjects and Zephyr EBV Subjects, 50.1 and 51.5 respectively ($p = 0.3236$). Baseline mMRC dyspnea scores were identical for Control Subjects and Zephyr EBV Subjects, 1.7 and 1.7 respectively ($p = 0.7748$).

Baseline exercise tolerance was the same between the two study groups. The Control Subjects had a slightly lower peak workload on cycle ergometry (43.2 versus 45.0 watts, $p = 0.71$). However, the Control Subjects showed a slightly longer 6MWT (350.9 versus 333.9 meters, $p = 0.15$). Dyspnea and fatigue were rated on a scale from 0 to 10 during exercise testing (Borg Test) at baseline, and there were no significant differences in dyspnea or fatigue scores before or after performing the 6MWT.

High Resolution Computed Tomography (HRCT) baseline characteristics were the same between the two study groups. These characteristics included disease distribution, volume distribution, target lobe disease, target lobe volume, and fissure integrity.

ZEPHYR EBV IMPLANTATION PROCEDURE (FROM SECTION 7.0):

The mean procedure duration—the time between bronchoscope insertion and bronchoscope removal—was 33.8 minutes (median 28 minutes, range 6 to 100).

Target lobes were defined by pre-procedural imaging assessments. Target lobes were largely in the upper lobes (76.6%) and predominantly in the right side (61.6%). The right

upper lobe was the target in 52.3% of Zephyr EBV Subjects, the right lower lobe in 9.3%, the left upper lobe in 24.3%, and the left lower lobe in 14.0%.

Conscious sedation was used during the implantation procedure in 71.5% of subjects, with the remaining 28.5% having general anesthesia. This choice of anesthesia was reflected in the proportion of subjects who were intubated (35.1%) or ventilated (29.9%) during the implantation procedure. Three (3) Zephyr EBV Subjects had a rigid bronchoscope used during the Zephyr EBV implantation procedure, the remaining 211 procedures involved only flexible bronchoscopy.

The mean number of valves placed per Zephyr EBV Subject was 3.8 (median 4, range 1 to 9). Acute Technical Success—determined by the implanting site at the time of the procedure, based on the Investigator's assessment of complete exclusion of the target lobe—was found in 94.9% of subjects.

Of the 214 Zephyr EBV Subjects who received one or more valves during the initial study procedure, 96 subjects had a total of 143 valves removed during the procedure. In 89 of these 96 subjects (92.7%), the valves removed during the procedure were successfully replaced with one or more valves, which led to Acute Technical Success (lobar exclusion) as reported by the site.

Of the 143 valves removed during the initial procedure, 92.3% were for valve positioning: 48.9% were placed too proximally, 19.6% too distally and 3.5% were too small for the selected airway. Other removals for sizing or positioning reasons accounted for 20.3% of valves removed during the initial procedure and included: valve was dislodged while removing other valves, valves placed in wrong airway, first valve placed interfering with placement of other valves, valve was too large for the selected airway, and incomplete exclusion. Valve or deployment reasons for removal accounted for 7.7% of valves removed during the initial procedure and included: valve appeared non-functional, valve did not deploy properly, valve loaded and deployed backwards, and duckbill appeared inverted.

There were device malfunctions in 21 (9.8%) of Zephyr EBV procedures, and 1 device malfunction in a follow-up procedure to replace an expectorated valve. For the total of 22 subjects with any device malfunction, 35 devices were reported as malfunctioning (18 EBVs, 15 EDCs and 2 ELSs). The majority of the malfunctions were associated with Loading Failures and Delivery Failure due to Anatomical Constraints.

Overall the Zephyr EBV system was easy to use, reliable and successful in achieving lobar exclusion at the time of the initial procedure.

PRIMARY AND SECONDARY EFFECTIVENESS OUTCOMES (FROM SECTION 8.0):

A primary objective of the VENT Pivotal Trial was to assess the effectiveness of the Zephyr EBV in treating patients with severe heterogeneous emphysema. This was to be assessed by determining the FEV_1 and 6MWT values at baseline and at 6 months, and to compare the percentage change from baseline in these tests between the Control Subjects and the Zephyr EBV Subjects. Both measures were to be tested using a one-sided superiority test at a significance level of 0.025, and then be confirmed by multivariate testing.

The VENT Pivotal Trial met its primary effectiveness outcome, with a significantly better percent change in both FEV_1 and 6MWT in Zephyr EBV Subjects when compared to Control Subjects at 6 months of follow-up. These significant differences existed whether the analysis was performed with multiple imputation for missing values or with completed cases only. Treatment with Zephyr EBV remained as a significant factor in both the FEV_1 and 6MWT multivariate models, confirming the univariate finding.

Primary Effectiveness Outcome		**Delta (95% CI)**	**p value**
ITT	**Percent Change in FEV_1**	6.8 (2.1, 11.5)	**0.002**
	Percent Change in 6MWT	5.8 (0.5, 11.2)	**0.019**
CC	**Percent Change in FEV_1**	7.2 (3.2, 11.2)	**< 0.001**
	Percent Change in 6MWT	5.8 (1.3, 11.7)	**0.008**

The VENT Pivotal Trial met its 4 secondary effectiveness outcomes, with significantly better outcomes at 6 months in the St. George's Respiratory Questionnaire (SGRQ) Score, the modified Medical Research Council Dyspnea Scale (mMRC), the maximum workload during cycle ergometry, and the use of supplemental oxygen in Zephyr EBV Subjects when compared to Control Subjects.

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2° Outcome Measures		Delta (95% CI)	p value
ITT	Change in SGRQ (points)	-3.4 (-6.6, -0.3)	**0.0167**
	Change in mMRC (points)	-0.26 (-0.49, -0.02)	**0.0183**
	Change in Max. Workload (watts)	3.8 (0.2, 7.4)	**0.0203**
	Change in Supplemental O_2 (L / day)	-12.0 (–76.7, 52.7)	**0.0198**
CC	Change in SGRQ (points)	–3.40 (–6.61, –0.18)	**0.0192**
	Change in mMRC (points)	–0.30 (–0.56, –0.05)	**0.0108**
	Change in Max. Workload (watts)	5.0 (0.0, 5.0)	**0.0044**
	Change in Supplemental O_2 (L / Day)	-100.1 (-318.6, 118.4)	0.1837

PRIMARY SAFETY OUTCOME (FROM SECTION 9.0):

At 6 months of follow-up, Control Subjects had a 1.2% (1 / 87) rate of MCCs compared to Zephyr EBV Subjects who had a 6.1% (13 / 214) rate of MCCs, a difference that was not significant (p = 0.0748, Fisher's exact test). This difference was primarily driven by a trend to greater 6 month mortality in the Zephyr EBV Subjects with 6 deaths: 3 from respiratory failure, one from cancer, one from ischemic colitis and 1 from massive hemoptysis, of which only the death from hemoptysis was related to the device.

All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects (p = 0.8763, log rank test).

In the second six months of follow-up, the MCC rate in Zephyr EBV Subjects (4.7%) and the MCC rate in Control Subjects (4.6%) were almost identical. Over all, with 12 months of follow-up, the MCC rate for Control Subjects (4.6%) and for Zephyr EBV Subjects (10.3%) were not significantly different (p = 0.1724, Fisher's exact test).

ADDITIONAL PRE-SPECIFIED ANALYSES (FROM SECTION 10.0):

Additional effectiveness analyses were performed for residual volume, diffusing capacity, Quality of Wellbeing and the BODE Index. Although Zephyr EBV Subjects trended higher in all these measures, only the BODE Index showed an improvement that was significant (p = 0.0024).

Technical Success (complete lobar exclusion by HRCT at 6 months) was achieved in 56.2% of Zephyr EBV Subjects, with the majority of Technical Failures (78.8%) occurring when one or more valves were found to be in place but not fully occlusive.

Rehospitalization rates through 6 months were 16.1% for Control Subjects and 27.1% for Zephyr EBV Subjects, a difference that bordered on significant ($p = 0.0522$). For the period from 6 to 12 months, this difference began to converge, with 12.6% for Control Subjects and 19.6% for Zephyr EBV Subjects. Most of this difference occurred during the first quarter of follow-up in subjects who required removal of one or more Zephyr valves.

Technical Success subjects had an FEV_1 improvement that was 9.4 percentage points higher in subjects with Technical Success compared with subjects with Technical Failure.

High Heterogeneity subjects demonstrated a substantially larger therapeutic benefit compared with the study population as a whole: FEV_1 improvement at 6 months was 12.3 percentage points higher, and 6MWT at 6 months was 14.4 percentage points higher, in High Heterogeneity Zephyr EBV Subjects compared with High Heterogeneity Control Subjects.

Subjects with Complete Fissure Integrity had an FEV_1 improvement that was 16.2 percentage points higher than subjects with Incomplete Fissure Integrity.

RESPONDER ANALYSES (FROM SECTION 11.0):

Responder analyses for the VENT Pivotal Study effectiveness measures of FEV_1 and 6MWT demonstrated that a substantially larger proportion of Zephyr EBV Subjects achieved clinically important levels of improvement than did Control Subjects.

Outcome Measure	Relative Rate (95% CI)
$FEV_1 \geq 0\%$	1.4 (1.1 – 1.9)
FEV_1 High Heterogeneity≥ 0%	2.0 (1.3 – 3.2)
$FEV_1 \geq 15\%$	2.2 (1.1 – 4.5)
FEV_1 High Heterogeneity≥ 15%	2.8 (1.2 – 6.7)
6MWT≥ 0%	1.3 (1.0 – 1.7)
6MWT High Heterogeneity≥ 0%	1.8 (1.1 – 2.8)
6MWT≥ 15%	1.4 (0.8 – 2.5)
6MWT High Heterogeneity≥ 15%	2.4 (1.0 – 5.7)

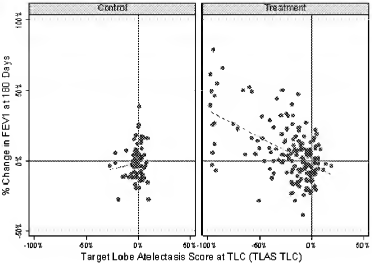
Responder analyses for the VENT Pivotal Study effectiveness measures of SGRQ, mMRC, maximum workload and the BODE Index all demonstrated that a substantially larger proportion of Zephyr EBV Subjects achieved clinically important levels of improvement than did Control Subjects.

Outcome Measure	MCID	Relative Rate (95% CI)
SGRQ	8 points	2.8 (1.3 – 5.7)
mMRC	1 point	1.8 (1.0 – 3.2)
Ergometry	10 watts	1.9 (1.0 – 3.7)
BODE Index	1 point	2.2 (1.2 – 3.8)

TREATMENT, VOLUME REDUCTION AND FEV1 (FROM SECTION 12.0):

Analyses of relevant study variables supported the primary rationale of Zephyr EBV treatment, which was that Zephyr EBV treatment led to reduction in target lobe volume reduction (TLVR), which in turn led to improvement in changes in pulmonary function at 6 months.

Zephyr EBV Subjects had a mean change in $TLAS_{TLC}$ at 6 months of −20.6% compared with Control Subjects (−1.7%, $p < 0.0001$). Reduction in TLVR at 6 months as measured by $TLAS_{TLC}$ was significantly associated with improved FEV_1 at 6 months ($r^2 = 0.2785$, $p = 0.000$):



The factors that were significantly associated with TLVR were Technical Success, complete fissure integrity and their combination, demonstrating the importance of exclusion of the target lobe. The factors associated with significantly improved FEV_1 at 6 months were Zephyr EBV treatment, Technical Success, complete fissure integrity, and the combination of Technical Success and complete fissure integrity.

<u>SAFETY PROFILE AT ONE YEAR (FROM SECTION 13.0):</u>

Mortality: all-cause mortality was similar in the two groups through one year of follow-up, with 3.5% (95% CI 0.7 – 9.8%) of Control Subjects and 3.7% (95% CI 1.6 – 7.2%) of Zephyr EBV Subjects dying of any cause during the year. This difference was not significant.

COPD / Emphysema Adverse Events: The VENT Pivotal Study revealed the high degree of pulmonary morbidity present in subjects with severe heterogeneous emphysema, with 77.6% of Zephyr EBV Subjects and 62.1% of Control Subjects having one or more COPD / emphysema category adverse events; this difference was significant (p = 0.0095). This difference was driven by the following subcategories of adverse events: COPD exacerbation (72.4% Zephyr EBV Subjects and 57.5% Control Subjects, p = 0.0141, Other Pulmonary Infection (8.4% compared with 1.2% respectively, p = 0.0174), Increased SOB (9.8% compared with 2.3% respectively, p = 0.0295) and Altered ABGs (8.4% compared with 1.2% respectively, p = 0.0174).

When <u>serious adverse events</u> are examined only COPD with exacerbation is significantly different, with an 23.4% rate for Zephyr EBV Subjects and a 10.3% rate for Control Subjects (p = 0.0101).

Pulmonary / Thoracic Adverse Events: The rate of these adverse events was higher in Zephyr EBV Subjects, 52.8%, compared with Control Subjects, 9.2% ($p < 0.0001$). This difference was driven by the following subcategories of adverse events: hemoptysis (42.1% Zephyr EBV Subjects compared with 2.3% in Control Subjects, $p < 0.0001$), and Noncardiac Chest Pain (16.4% compared with 3.5%, $p = 0.0018$). When serious adverse events are examined, only hemoptysis remains significantly more frequent in Zephyr EBV Subjects, 11.7%, compared with 0.0% in Control Subjects ($p = 0.0003$).

General / Other Adverse Events: The remaining categories of adverse events occurred somewhat more frequently in Zephyr EBV Subjects, 49.1%, compared with Control Subjects, 33.3% ($p = 0.015$). Rates that were higher in Zephyr EBV Subjects included: nausea and vomiting (often related to procedure sedation), headaches, sore throat, and similar minor complaints.

There are no significant differences in the rate of serious adverse events for General / Other adverse events.

Resolution of Adverse Events: Most of these adverse event and serious adverse event rates decline after the first three months of follow-up, suggesting that the passage of time and, when indicated, removal of one or more valves are effective responses to these events.

Valve Expectoration or Migration: Of 820 implanted valves at the completion of the initial procedure, 23 (2.8%) migrated or were expectorated in 17 subjects between Days 0 and 274 without significant sequelae, and 14 subjects had at least one of these valves replaced during study follow-up.

Pneumonia Distal to Valves: 9 Zephyr EBV Subjects (4.2%) had pneumonia distal to valves and received drug therapy (9) and valve removal (3). Eight (8) of the 9 resolved during the study follow-up period and one subject, with onset on Day 356, was still under treatment at the end of the 1-year study follow-up period.

Massive Hemoptysis: One Zephyr EBV Subject experienced dyspnea and hemoptysis between Days 0 and 8, and then presented in cardiorespiratory arrest on Day 8 and died thereafter of hypoxic brain damage. Autopsy revealed bullous emphysema, 4 intact and well-positioned valves, and no obvious source of bleeding.

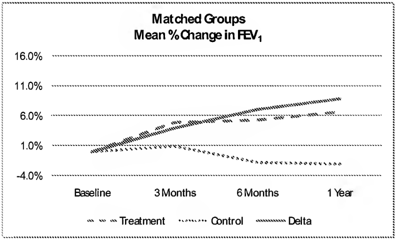
Valve Treatment for Persistent Air Leak: One Zephyr EBV Subject developed complete left pneumothorax on Day 1, with only partial resolution after chest tube placement. Compassionate Use treatment with 2 additional valves in the superior segment of the left lower lobe significantly reduced but did not eliminate the air leak until 8 days later.

Valve Removal During Study Follow-Up: Thirty one (31, 14.5%) Zephyr EBV Subjects had one or more valves removed after the initial procedure. Eighty five (85) of 87 valves attempted were successfully removed (97.7%). Of these 31 subjects, 25 (80.6%) had resolution of the reason for the intervention following valve removal.

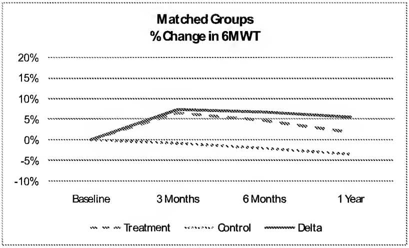
OUTCOME MEASURES AT ONE YEAR (FROM SECTION 14.0):

Although the VENT Pivotal Study was not designed or sized to test significance of effectiveness measures at 1 year of follow-up, outcome measurements continued to favor Zephyr EBV Treatment over the Control through this time point.

From matched grouped comparisons of results at 3 months, 6 months, and 1 year FEV1 appears to continue to improve in the Zephyr EBV Treatment Group through the entire 1 year follow-up. The treatment effect remained statistically-significant at 1 year.



Zephyr EBV Treatment Group benefit in 6MWT appears to peak at 3 months while retaining most of the net benefit through 1 year for those Subjects with matched data. However, the treatment effect was not statistically-significant at 1 year.



DISCUSSION AND CONCLUSION (SECTION 15.0):

Overview: The VENT Pivotal Trial was a randomized, controlled, multi-center trial that enrolled subjects with severe heterogeneous emphysema to assess the safety and effectiveness of the Emphasys Endobronchial Valve (Zephyr EBV) and procedure compared to optimal medical management. Zephyr EBV Subjects underwent bronchoscopic Zephyr EBV implantation and both Zephyr EBV Subjects and Control Subjects received optimal medical management. Six month follow-up for all subjects included assessment of a variety of relevant pulmonary and general outcome measures as evaluated by specific spirometry, body plethysmography, diffusing capacity, QoL and exercise tests; a 12 month follow-up visit was also performed. The co-primary effectiveness outcomes were the percent changes in both FEV_1 and 6MWT in Zephyr EBV Subjects compared to Control Subjects determined at the 6 month follow-up visit; superiority had to be demonstrated in both measures to meet the outcome. The primary safety outcome was the Major Complication Composite at 6 months.

Validity of Results: The VENT Pivotal Trial enrolled 321 subjects and randomization resulted in highly comparable treatment groups with severe, heterogeneous emphysema (101 Control Subjects, 220 Zephyr EBV Subjects). Study subjects were assessed, treated and followed under the provisions of the approved study protocol, with a high degree of subject, device and imaging accountability. Monitoring procedures, data handling and statistical practice ensured that the results reported in this Clinical Study Report are valid scientific evidence.

Procedure: The bronchoscopic initial implantation procedure was quick (33.8 minutes) with 71.5% of subjects treated with conscious sedation only. A mean of 3.8 valves were implanted per Zephyr EBV Subject, with Acute Technical Success in 94.9%. Valves

were frequently removed and replaced without difficulty during implantation procedures, allowing the operator to achieve optimal positioning.

Primary Effectiveness Outcome: The VENT Pivotal Trial met its co-primary outcomes, with a significantly better percent change in both FEV_1 and 6MWT in Zephyr EBV Subjects when compared to Control Subjects at 6 months of follow-up. These significant differences existed whether the analysis was performed with multiple imputation for missing values or with completed cases only, and were confirmed by pre-specified multivariate analysis.

Multiple Imputation Primary Effectiveness Outcomes	Delta (95% CI)	p value
Percent Change in FEV_1	6.8 (2.1, 11.5)	0.002
Percent Change in 6MWT	5.8 (0.5, 11.2)	0.019

Secondary Effectiveness Outcomes: All four secondary effectiveness outcomes were met, with the changes in the St. Georges Respiratory Questionnaire, the Modified Medical Research Council Dyspnea Scale, the maximum workload measured by cycle ergometry, and the use of supplemental oxygen, all significantly better in the Zephyr EBV Subjects when compared with the Control Subjects.

Secondary Effectiveness Outcomes - ITT	Delta (95% CI)	p value
Change in SGRQ (points)	–3.4 (–6.6, –0.3)	0.0167
Change in mMRC (points)	–0.26 (–0.49, –0.02)	0.0183
Maximum workload (watts)	3.8 (0.2, 7.4)	0.0203
Change in Supplemental O_2 (L / day)	–12.0 (–76.7, 52.7)	0.0198

Primary Safety Outcome: At 6 months of follow-up, Control Subjects had a 1.2% rate of Major Complication Composite events (MCCs) compared with 6.1% for Zephyr EBV Subjects, a trend that was not significant ($p = 0.0748$). This difference was primarily driven by a trend to greater 6 month mortality in the Zephyr EBV Subjects with 6 deaths: 3 from respiratory failure, one from cancer, one from ischemic colitis and 1 from massive hemoptysis, of which only the death from hemoptysis was related to the device.

All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects ($p = 0.8763$, log rank test). The MCC rate in the second 6 months of follow-up was almost identical: 4.6% for Control Subjects and 4.7% for Zephyr EBV Subjects. Zephyr EBV treatment was not significantly associated with the occurrence of MCCs through 6 months.

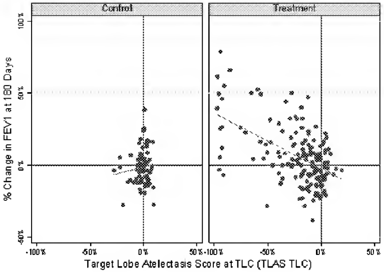
Additional Pre-Specified Analyses: The change in BODE Index was significantly better in the Zephyr EBV Subjects than Control Subjects ($p = 0.0024$). Percent changes in residual volume and diffusing capacity were slightly but not significantly better in Zephyr EBV Subjects, and the Quality of Wellbeing instrument revealed no difference between the groups.

Technical success (complete lobar exclusion) was found in 56.2% of Zephyr EBV Subjects on HRCT at 6 months. There was a trend towards higher hospitalization rates for Zephyr EBV Subjects (27.1%) compared with Control Subjects (16.1%) through 6 months, which was borderline significant ($p = 0.0522$); this difference appeared to be driven largely by study-related valve removal procedures and diminished during the last 6 months of follow-up.

Pre-specified subgroup analyses showed that Zephyr EBV Subjects with Technical Success (HRCT-confirmed target lobe exclusion at 6 months) had a greater mean percent change in FEV_1 (9.4%) compared with Zephyr EBV Subjects without Technical Success (0.0%) , $p = 0.0009$. Zephyr EBV treatment effect was substantially greater in High Heterogeneity subjects for both primary outcome measures: Zephyr EBV Subjects had higher FEV_1 (10.1%) and 6MWT (7.3%) changes compared with Control Subjects FEV_1 (−2.2%, $p < 0.0001$) and 6MWT (−5.9%, $p = 0.0003$). Complete fissure integrity also was associated with a greater treatment response for FEV_1, with Zephyr EBV Subjects having a 13.5% improvement compared with Control Subjects -2.7% (delta 16.2%, $p < 0.0001$).

Clinical Importance (Responder Analyses): Responder analyses performed at generally accepted levels of minimal clinically important differences (MCIDs) on key outcome measures revealed that single lobe Zephyr EBV treatment confers a consistent pattern of clinical benefit for FEV_1, 6MWT, SGRQ, mMRC, maximum workload by cycle ergometry and the BODE Index, all key clinical indicators of disease status.

Treatment, Volume Reduction and FEV_1: Treatment with Zephyr EBV, achieving Technical Success (complete lobar exclusion) and the presence of complete fissure integrity are all associated with significantly greater target lobe volume reduction (TLVR) and with significantly better FEV_1 outcomes at 6 months.



Safety Profile: A review of the adverse event (AE) profile of the Zephyr EBV reveals that implanted subjects had higher rates of emphysema related conditions, including such manifestations as COPD exacerbations, other pulmonary infections, increase shortness of breath and hypoxemia. Use of the Zephyr EBV was associated with higher rates of hemoptysis and atypical chest pain. When considering serious adverse events (SAEs) only COPD exacerbations requiring hospitalization and hemoptysis emerged as significantly more frequent events. For both AEs and SAEs, event rates in the Zephyr EBV Subjects tended to decline during study follow-up and approach the rates of the Control Subjects. These declines in adverse event rates appeared to be independent of valve removals.

Key aspects of the Zephyr EBV safety profile that have emerged from the VENT Pivotal Trial include the following characteristics:

- Use of the Zephyr EBV was associated with increased rates of COPD related adverse events, hemoptysis, atypical chest pain and perhaps rehospitalization through 1 year of follow-up.
- Granulation tissue, valve migration, and pneumonia distal to the valve are adverse events that are specifically related to the use of this device.
- These phenomena diminish with time.
- The device can be safely removed with a high degree of success, and when valve removal is performed as a result of an adverse event, the adverse event generally resolves.
- There was no difference in all-cause mortality between the Control Subjects and Zephyr EBV Subjects over the 1-year study follow-up.

Outcome Measures at One Year: Although the VENT Pivotal Study was not designed or sized to test significance of effectiveness measures at 1 year of follow-up, outcome measurements continued to favor Zephyr EBV Treatment over the Control through this time point. These results were confirmed by responder analysis and matched pairs analysis.

Conclusion: The VENT Pivotal Trial results demonstrate that unilateral treatment of severe heterogeneous emphysema in medically optimized subjects achieved substantial additional improvement in a variety of outcomes including FEV_1 and 6MWT over that achieved by approved medical treatments alone. This level of additional improvement in maximally treated, severely ill subjects is clinically important. Such findings constitute valid scientific evidence demonstrating the effectiveness of the Zephyr EBV device in improving important subjective and objective measures of health in a population of subjects with severe heterogeneous emphysema. While there are several clear risks of the use of the Zephyr EBV device, these are generally minor, tend to diminish over time, and usually resolve after device removal. Use of the Zephyr EBV in patients with severe heterogeneous emphysema provides an important palliative benefit that exceeds the attendant risks.

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LIST OF ABBREVIATIONS AND ACRONYMS

6MWT	Six minute walk test
95% CI	95 percent confidence interval
AE	Adverse event
BODE Index	BMI / Airway Obstruction / Dyspnea / Exercise Capacity Index
CC	Completed Case
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CQ	Corrections/Query form
CRF	Case Report Form
CRL	Core Radiology Laboratory
CSR	Clinical Study Report
CT	Computed tomography (scan)
CXR	Chest X-ray
DL_{CO}	Diffusing capacity (lung) for carbon monoxide
DS	Density Score
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
ERV	Expiratory reserve volume
ES	Emphysema Score
FDA	Food and Drug Administration
$FEF_{25-75\%}$	Forced expiratory flow rate (middle 50% of exhaled volume)
FEV_1	Forced expiratory volume (one second)
FEV_1 % predicted	Forced expiratory volume (one second) as a percent of predicted
FiO_2	Fraction of inspired oxygen
FRC	Functional reserve capacity
FVC	Forced vital capacity
GCP	Good Clinical Practice
HRCT	High Resolution Computed Tomography (scan)
HS	Heterogeneity Score
IC	Inspiratory capacity
IDE	Investigational Device Exemption
IRB	Institutional Review Board

ITT	Intent-to-treat
LTFU	Lost to follow-up
LVEF	Left ventricular ejection fraction
LVRS	Lung volume reduction surgery
MCC	Major Complication Composite
MI	Myocardial infarction
mm Hg	Millimeters of mercury (pressure)
mMRC	Modified Medical Research Council Dyspnea Scale
MVV	Maximal voluntary ventilation
NETT	National Emphysema Treatment Trial
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
P_{EFR}	Peak expiratory flow rate
P_{IFR}	Peak inspiratory flow rate
PFT	Pulmonary function testing
PVC	Premature ventricular contraction
QoL	Quality of Life
QWB	Quality of Well Being (Scale)
RV	Residual volume
SAE	Serious adverse event
SAT	Arterial blood saturation with oxygen
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
SIRS	Systemic inflammatory response syndrome
SVT	Supraventricular tachycardia
Target Lobe	The lobe of the lung targeted for treatment by HRCT algorithm prior to randomization. After randomization to the Zephyr EBV group, the lobe which is treated with Zephyr EBV device(s).
$TLAS_{RV}$	Target lobe atelectasis score at residual volume
$TLAS_{TLC}$	Target lobe atelectasis score at total lung capacity
TLC	Total lung capacity
TLVR	Target Lobe Volume Reduction
UADE	Unanticipated adverse device effect
VQ	Ventilation perfusion (scan)
VTG	Volume of thoracic gas
Zephyr EBV	Zephyr Endobronchial Valve

1.0 INTRODUCTION

1.1 Disease Information

The estimated prevalence of emphysema in the US population in 2004 was 3.5 million people. Half of emphysema patients in the U.S. are 65 years of age or older and 39% are between the ages of 45 and 65. Emphysema is therefore a clinically disabling disease which can adversely affect economic well-being.[1]

Emphysema is a chronic lung disease characterized by the permanent, abnormal distention of air spaces distal to the terminal bronchiole with destruction of the alveolar septa. It is often coexistent with chronic bronchitis, and is most commonly caused by long term cigarette smoking, although air pollution, occupational exposure, infection and familial and genetic factors have also been implicated.

As emphysematous destruction progresses, the loss of alveolar and capillary structures result in reduced lung function. Breathlessness leads to reduced activity and a secondary reduction in cardiovascular conditioning. This in turn exacerbates breathlessness and the negative cycle continues to complete debilitation. Intervening complications include infection, including COPD exacerbation and recurrent pneumonia.

There is no known intervention which can halt or reverse the underlying disease of emphysema, and all treatments to date are palliative. These treatments include continuous supplemental oxygen therapy and medications such as bronchodilators, steroids and mucolytics.

Recent trials of more aggressive interventions attempting to alter lung mechanics have been tried. The National Emphysema Treatment Trial (NETT) showed that surgical removal of the most disease parts of the lungs—known as lung volume reduction surgery (LVRS)—can improve lung function and possibly even survival in carefully selected subsets of patients.[2-5] Use of this procedure has been quite limited, given the strict selection criteria and the significant peri-operative morbidity and mortality.

Emphysema remains a significant clinical challenge. Pharmacotherapy and occasionally surgery have clear palliative benefit, but more effective and safer interventions are needed to better serve these patients. The VENT Pivotal Trial of the Emphasys Zephyr Endobronchial Valve (Zephyr EBV) was undertaken to test the safety and effectiveness of a bronchoscopically inserted one-way valve in the treatment of patients with emphysema.

1.2 Emphasys Device Information

Emphasys Medical has developed a bronchoscopic approach to block the inspiratory airflow into targeted, hyperinflated regions of the lung, while permitting exhaled gas to escape. This approach may provide some of the clinical benefits of lung volume reduction surgery (LVRS) without the high risks and costs associated with such an invasive surgical procedure. It may also provide benefits that are not realized through LVRS by preserving lung tissue.

The Emphasys Zephyr Endobronchial Valve (Zephyr EBV) incorporates a one-way valve that is implanted in a bronchial lumen. The one-way valve is supported by a self-expanding retainer that secures the implanted Zephyr EBV in place during all physiological conditions, including coughing. The implanted Zephyr EBV allows air to be vented from the isolated lung segment under normal exhalation pressure, and prevents air from refilling the isolated lung area during inhalation. The Zephyr EBV is provided in two sizes, each intended for a different range of target bronchial lumen diameters.

1.3 Rationale for Endobronchial Valve Treatment

The rationale for using a one-way valve to treat patients with emphysema stems from results of lung volume reduction surgery (LVRS). With LVRS, the objective is to surgically eliminate dysfunctional, over-inflated regions of lung.[6] The National Emphysema Treatment Trial (NETT), along with other studies, has shown that LVRS can offer relief to some patients suffering from emphysema when other treatments have failed.[2 – 5, 7 - 11]

This paradoxical affect of improving lung function by removing (or isolating) lung tissue demonstrates that breathlessness due to emphysema is a function of mechanical compromise in addition to loss of gas-transfer surface area. In some patients, the mechanical compromise is the primary cause of their pulmonary incapacitation and these patients may benefit by addressing the impact of severely emphysematous lung upon the ability to ventilate more normal pulmonary tissue.

Results similar to surgical removal of diseased lung sections during LVRS have also been obtained by plication (folding) and stapling without tissue removal.[12 - 15] These results suggest it is modification of the dysfunctional lung region which is key, and that similar results may be possible without actual resection of tissue.

Because both approaches reduce trapped gas, Emphasys Medical hypothesized that similar results could be achieved bronchoscopically. This approach may provide the clinical benefits of lung volume reduction surgery in a minimally invasive and potentially

reversible manner, thus reducing the morbidity and mortality associated with an open surgical procedure such as LVRS. [16 - 18]

The intended physiological and clinical cascade resulting from placing a valve in the airways leading to diseased lung tissue includes reduced hyperinflation and improved breathing mechanics, improved airflow and gas exchange in viable lung segments, and improved lung function and clinical status.

The placement of endobronchial valves is intended to improve the respiratory mechanics in patients with emphysema by preventing airflow to lung regions with poor elastic recoil. In addition, the valves help to improve gas transfer in the lung by preferentially directing inspiratory flow to the healthier lung sections and by allowing these regions to expand more fully. The resulting lung function improvements should enable patients to increase their daily activity leading to a more active lifestyle and improved QoL.

Endobronchial valves do not treat the underlying pathology and therefore do not slow the progression of the disease or reduce a patient's susceptibility to COPD exacerbations or chest infections that are common in these patients.

1.4 Preclinical and Clinical Studies

The Emphasys Endobronchial Valve underwent extensive testing prior to its use in the VENT Pivotal Trial. Biocompatibility testing under FDA guidelines demonstrated that the device was biocompatible for its intended use in the human tracheobronchial tree. *In vivo* assessments were used to optimize device design and to demonstrate its performance before use in human subjects. In particular, long term studies in sheep demonstrated that the device could be reliably placed in the tracheobronchial tree, that it caused volume reduction in the experimentally created obstructed lung segments, that it did not migrate and that it could be removed safely. Most animals had no signs of distal infection; a small proportion had signs of mild subclinical pneumonia.

Pilot clinical studies were performed with several device iterations. At the time the VENT Pivotal Trial began, 71 subjects with advanced emphysema at 9 international sites had been followed post EBV placement. Thirty-eight of these subjects had been treated with complete lobar exclusion. For this 38 subject subset, baseline mean FEV_1 was 31% of predicted, the 6MWT averaged 300 ± 128 meters, DL_{CO} averaged 42% of predicted and RV average 280% of predicted. After 90 days of follow-up, mean FEV_1 had improved from the baseline value by 15%, mean 6MWT by 20%, mean DL_{CO} by 14% and mean RV had decreased by 2%.

Adverse events in these subjects were consistent with the severity of their illness. There were two deaths during study follow-up. One subject died during the first month post

procedure, when valve-related post-obstructive pneumonia did not resolve after EBV removal. One subject died at 161 days post-procedure due to pneumonia in an untreated lobe. In the first 90 days post-procedure, two (2) pneumothoraces required surgical intervention, two (2) pneumothoraces lasted longer than 7 days, and six (6) other pneumothoraces were reported, some requiring chest tubes. There were 12 reports of COPD exacerbation, four reports of valve removal and one pleural effusion.

Overall, the morbidity and mortality of the Zephyr EBV procedure compared favorably to a meta-analysis of LVRS data.[19] Early mortality (from 0 to 30 days) was 2.6% compared to LVRS (2.5 to 7.0%), prolonged air leak was 2.6% compared to LVRS (30 to 48%), surgical exploration was required in 5.3% compared to LVRS (2.5 to 10%), respiratory failure occurred in 0% compared to LVRS (2 to 13%) and pneumonia occurred in 2.6% compared to LVRS (9 to 22%). Overall the per-patient rate of these serious complications was 13.2% compared to the mean estimate for LVRS of 73%.

These data suggested a favorable risk-benefit ratio for this novel minimally invasive palliation for severely emphysematous patients, and the VENT Pivotal Trial was designed and approved by the FDA. The remainder of this document details the study's design and results.

2.0 ETHICAL AND REGULATORY CONSIDERATIONS

2.1 Study Responsibility

Emphasys Medical, Inc., the Study Sponsor, was responsible for the overall conduct of the trial. The Sponsor conducted the clinical trial in compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements. The Sponsor designed and implemented study materials to support the trial including Case Report Forms (CRFs). Full-time Sponsor personnel followed approved Standard Operating Procedures in all study activities, including site selection, start-up and regulatory document maintenance activities as well as training of clinical site personnel. Data monitoring and site management were performed by full time Clinical Research staff and contractors. Data management activities were performed directly by a full-time data management team who created a dedicated study database and managed the data, processing, review, query, validation and data lock activities.

The Core Radiology Laboratory (CRL), provided by MedQIA in association with the UCLA David Geffen School of Medicine (Los Angeles, CA), was responsible for implementing standardized HRCT image collection at each investigational site. At enrollment, the CRL performed quantitative image analysis of screening HRCT scans to determine subject eligibility status. For each eligible subject the CRL determined the target lobe based on the VENT Pivotal Trial protocol requirements. Throughout the study, the CRL worked with investigational sites to ensure appropriate quality control measures including collecting and analyzing "phantom" HRCT scans.

Richard P. Chiacchierini Associates provided statistical support for the VENT Pivotal Trial. These activities included helping to write and revise the Statistical Analysis Plan as well as carrying out the actual analyses. This group was also responsible for the preparation of the final statistical reports associated with the trial.

2.2 Subject Confidentiality

Subject confidentiality was maintained throughout the clinical study. Once informed consent was obtained, subjects enrolled in the study were assigned a unique identifier indicating the site number, the subject number and the subjects' initials. All identifiers were listed on the patient screening log kept at each site. Any documents received by Sponsor to support and/or provide source document verification were redacted and assigned the appropriate subject identifier. All other unique identifiers, for example, Social Security numbers, addresses, etc. were also redacted as appropriate.

All information and data sent to Emphasys Medical concerning subjects or their participation in this study was considered confidential. All data used in the analysis and reporting of this evaluation was used in a manner without identifiable reference to any subject enrolled in the study. Hard copies of all study documentation including CRFs were kept in a locked, secure location. Computer access was password protected and permitted in variable levels according to responsibility.

2.3 Informed Consent and Institutional Review Boards (IRBs)

All informed consent documents required prior IRB approval. Signed written informed consent was mandatory for all study subjects and was obtained prior to initiation of any study specific procedures in the VENT Pivotal Trial. Informed consent was obtained in accordance with FDA regulation 21 CFR Part 50 except for protocol deviations as noted. Each site provided Emphasys Medical with a copy of their original IRB approval letter and the IRB approved consent form. Documentation of continuing IRB annual renewals were provided as appropriate. A sample of the most current informed consent document is included in Appendix 7-5-5.

2.4 Operations Committee

The Operations Committee approved the final trial design and protocol issued to the Data and Safety Monitoring Board (DSMB) and the clinical sites. This committee was responsible for the day-to-day administrative management of the trial, and met as needed to monitor subject enrollment, clinical site progress, and protocol compliance. The Operations Committee was also responsible for reviewing this Clinical Study Report.

2.5 Data and Safety Monitoring Board (DSMB)

The DSMB functioned in accordance with applicable regulatory guidelines, and consisted of a statistician and specialty physicians with relevant knowledge and skills. The DSMB was responsible for making recommendations to the Operations Committee regarding outcome analysis and any potential situations in which patient safety, patient welfare, or the scientific adequacy of the study were at risk. The DSMB also had responsibility for making confidential recommendations to the Operating Committee regarding study continuation or termination based on established safety stopping rules, but this was not necessary during this investigation. The DSMB charter and meeting minutes can be found in Appendix 7-2.

2.6 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) consisted of Pulmonologists and Thoracic Surgeons who were not otherwise participating in the study and was a distinct and separate group from the DSMB. The CEC met regularly throughout the trial to review

and adjudicate all Adverse Events. The CEC was blinded to Investigator and institution. The CEC charter and meeting minutes can be found in Appendix 7-3.

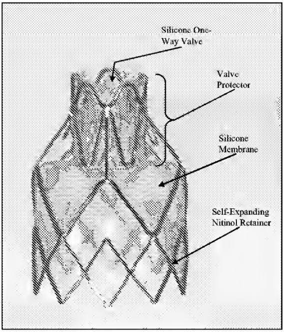
3.0 INVESTIGATIONAL DEVICES

The investigational devices included the Emphasys Zephyr Endobronchial Valve (Zephyr EBV), and the Zephyr Endobronchial Delivery System which consisted of the Zephyr Endobronchial Delivery Catheter (Zephyr EDC) and the Zephyr Endobronchial Loader System (Zephyr ELS).

3.1 Emphasys Zephyr Endobronchial Valve (Zephyr EBV)

The Emphasys Zephyr Endobronchial Valve (Zephyr EBV) is a one-way, silicone, duckbill valve mounted in a nickel-titanium (Nitinol), self-expanding retainer that is covered with a silicone membrane, as shown in Figure 1. The Zephyr EBV comes in two sizes, 4.0 mm to 7.0 mm and 5.5 mm to 8.5 mm, allowing bronchial lumens with diameters from 4.0 mm to 8.5 mm to be treated.

Figure 1 Photograph: Emphasys Zephyr Endobronchial Valve (EBV)



The Zephyr EBV is designed to be implanted into targeted bronchial lumens within the lungs of patients with advanced emphysema. Once implanted, the retainer anchors the Zephyr EBV in place in the bronchial lumen. The silicone membrane covering the retainer provides a peripheral seal between the device and the bronchial wall, as shown below in Figure 2. The one-way valve blocks inhaled air flow into hyperinflated regions

of the lung distal to the device while allowing trapped gas to vent from the hyperinflated regions.

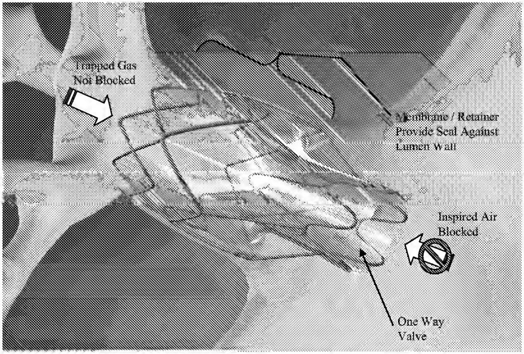


Figure 2 Diagram: Emphasys Zephyr Endobronchial Valve (EBV)

3.2 Zephyr Delivery Catheter and Zephyr Loader System

The Zephyr EBV is implanted in the target bronchial lumen using the Zephyr Endobronchial Delivery Catheter (Zephyr EDC), shown in Figure 3. Immediately prior to implantation, the Zephyr EBV is compressed and loaded into the distal end of the Zephyr EDC with the Zephyr Loading System (Zephyr ELS) (see Figure 4). The Zephyr EDC containing the loaded Zephyr EBV is advanced to the targeted bronchus through the working channel of a bronchoscope. Once the physician visually determines that the Zephyr EDC is at the target location, the Zephyr EBV is deployed. This deployment releases the compressed Zephyr EBV which expands and grips the bronchial lumen wall as illustrated in Figure 2. The Zephyr EBV can be removed bronchoscopically, if necessary, using standard flexible rats tooth grasping forceps.

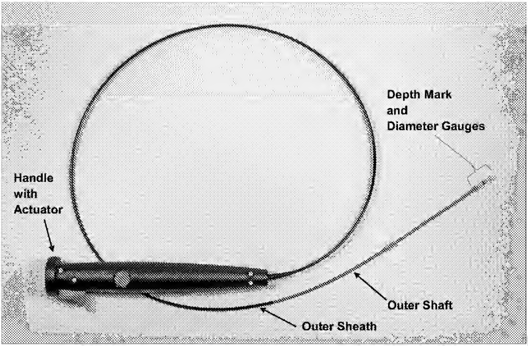


Figure 3 Photograph: Zephyr Endobronchial Delivery Catheter (Zephyr EDC)[*]

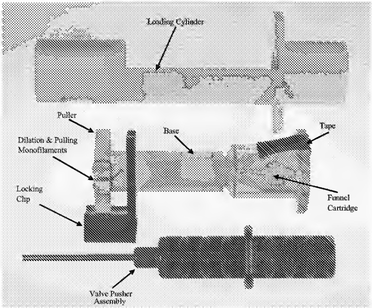


Figure 4 Photograph: Zephyr Endobronchial Loader System (Zephyr ELS)

[*] Depth Mark (also called "Marker Band") was implemented after completion of VENT (see original PMA Vol. 001, Page 80.

3.3 Handling and Storage

Emphasys Medical personnel oversaw the handling and storage of all investigational devices used in this study. Investigational devices were kept in segregated storage and shipped to approved investigational sites upon the completion of specified documentation. Device shipment receipt was documented by investigational sites and devices were placed in secure storage until used in the clinical study. When necessary, device returns and replacements were effected under a controlled and documented process, which included provisions for handling contaminated devices. Study monitors reviewed device handling and accountability at monitoring visits.

3.4 Accountability

Emphasys Medical supplied each Investigator with an adequate number of investigational devices for completion of the study. Emphasys Medical maintained records for each site of the number of devices shipped, used and returned. Throughout the study, device accountability records were regularly reviewed by the Emphasys Medical-appointed monitor. The Investigator was responsible for ensuring that the device accountability records were complete and up to date at all times.

4.0 STUDY DESIGN, MANAGEMENT AND ANALYSIS

4.1 VENT Pivotal Trial Overview

The primary objective of the VENT Pivotal Trial was to assess the safety and effectiveness of the Emphasys Endobronchial Valve (Zephyr EBV) and procedure compared to optimal medical management in subjects with heterogeneous emphysema.

The VENT Pivotal Trial was a randomized, controlled, multi-center trial enrolling 321 subjects with severe heterogeneous emphysema. The major study parameters—including the use of a control group, the target patient population, the primary and secondary outcomes and length of subject follow-up were all based on the recommendations of the FDA Advisory Panel Meeting held in February, 2003.

After granting informed consent and meeting enrollment criteria, study subjects all underwent history and physical examination, evaluation of pulmonary function and morphology including high resolution CT scanning (HRCT), a program of optimal medical management and aggressive pulmonary rehabilitation. Upon successful completion of this program subjects were randomized to either the Control or Zephyr EBV Treatment.

Zephyr EBV Subjects underwent bronchoscopic Zephyr EBV implantation under the provisions of the protocol which limited treatment to only one lobe (upper or lower lobe on one side). Complete exclusion of the target lobe was attempted by placing one or more Zephyr EBVs in lobar, segmental and / or subsegmental airways. Post-procedure, Zephyr EBV Subjects remained in the hospital and were observed for complications for at least 1 day.

Subsequent follow-up for all subjects consisted of assessment of a variety of relevant pulmonary and general outcome measures as evaluated by specific spirometry, body plethysmography, diffusing capacity, QoL and exercise tests. Follow-up and outcome assessments were scheduled for 2 – 3 days, 1 week, 1, 3, and 6 months, and 1 year.

The co-primary effectiveness outcomes were the percent change in both FEV_1 and 6MWT in Zephyr EBV Subjects compared to Control Subjects determined at the 6 month follow-up visit; superiority had to be demonstrated in both measures to meet the outcome. The primary safety outcome was the Major Complication Composite at 6 months.

4.2 Summary of Study Procedures

For a complete description of study procedures, please refer to the Study Protocol in Appendix 7-5-2 .

4.2.1 Subject Screening, Preparation and Randomization

Following informed consent, the first phase of screening consisted of historical and physical examination. Subjects meeting these initial screens underwent spirometry, plethysmography, diffusing capacity, exercise tolerance, and a high resolution computed tomography (HRCT) scan of the chest following the Core Radiology Lab (CRL) protocol. Disease categorization was performed by the CRL for each pulmonary lobe, resulting in quantitative assessments including a Density (or Emphysema) Score for each lobe and the volume of each lobe at maximal inhalation and maximal exhalation.

Screen subjects then underwent the Optimal Medical Management Program, consisting of smoking cessation support, treatment with bronchodilators and influenza and pneumococcal vaccination. Screen subjects also had aggressive pulmonary rehabilitation, involving upper and lower limb endurance and strength training in clinic and at home, and when necessary, oxygen therapy to maintain saturation at rest and exercise of > 90%. After the completion of pulmonary rehabilitation program, subjects were re-tested by spirometry, plethysmography, 6MWT, cycle ergometry, blood gases, and QoL instruments in order to screen for eligibility post pulmonary rehabilitation and to establish study baseline parameters.

Screen subjects who satisfactorily completed all these procedures and remained eligible for study participation were then randomized into two groups at a ratio of 2 to 1, with two subjects randomized to Zephyr EBV Treatment (Zephyr EBV Subjects) for each subject randomized to Control (Control Subjects), stratified by target lobe (upper versus lower) and exercise capacity (high versus low).

4.2.2 Inclusion / Exclusion Criteria

Candidates had to meet all of the following <u>inclusion criteria</u> to be eligible for enrollment in the study:

1. Subject diagnosed by HRCT Core Lab with eligible heterogeneous disease distribution (Section 6.7.5 of the protocol)
2. Age from 40 to 75 years
3. BMI < 31.1 kg / m^2 (men) or < 32.3 kg / m^2 (women)
4. FEV_1 < 45% of predicted value
5. Subject has provided written informed consent using a form that has been reviewed and approved by the IRB / EC

6. Stable with < 20 mg prednisone (or equivalent) daily
7. TLC > 100% predicted
8. RV > 150% predicted
9. $PaCO_2$ < 50 mm Hg (Denver < 55 mm Hg)
10. PaO_2 > 45 mm Hg (Denver > 30 mm Hg) on room air
11. Post rehabilitation 6MWT of > 140 meters
12. Plasma cotinine level < 13.7 ng / ml (or arterial carboxyhemoglobin < 2.5% if using nicotine products)
13. Nonsmoking for 4 months prior to initial interview and throughout screening
14. The subject agrees to all protocol required follow-up intervals
15. The subject has no child bearing potential OR a negative pregnancy test in a woman of childbearing potential
16. The subject is willing and able to complete protocol required baseline assessments and procedures

Candidates who met any of the following exclusion criteria were not eligible for enrollment in the study:

1. FEV_1 < 15% predicted value
2. DL_{CO} < 20% predicted value
3. Evidence of large bullae (encompassing > 30% of either lung) in a non-target lobe
4. An HRCT Density (Emphysema) Score of 4-4-4 in the right lung or 4-4 in the left lung
5. Unplanned weight loss of > 10% usual weight in 90 days prior to enrollment or total body weight < 70% of ideal body weight
6. Prior lung transplant, LVRS, Median sternotomy, bullectomy or lobectomy
7. Alpha-1 antitrypsin deficiency
8. Pleural or interstitial disease that precludes surgery
9. Clinically significant bronchiectasis
10. Pulmonary nodule requiring surgery
11. History of recurrent respiratory infections (> 1 hospitalization in the last year)
12. Clinically significant (> 4 tablespoons per day) sputum production
13. Fever, elevated white cell count, or other evidence of active infection
14. Dysrhythmia that might pose a risk during exercise or training
15. Congestive heart failure within 6 months and LVEF < 45%
16. Clinical suspicion or proven history of pulmonary hypertension
17. Evidence or history of cor pulmonale
18. Resting bradycardia (< 50 beats / min), frequent multifocal PVCs, complex ventricular arrhythmia, sustained SVT
19. History of exercise-related syncope

20. MI within 6 mo and LVEF < 45%
21. Evidence of systemic disease or neoplasia expected to compromise survival during 5-yr period
22. Any disease or condition that interferes with completion of initial or follow-up assessments
23. Subject is currently enrolled in another clinical trial or has been previously enrolled in the VENT Pivotal Trial for which protocol required follow up is not complete
24. Subject is unable to complete 3 minutes of unloaded pedaling on cycle ergometer

4.2.3 Zephyr EBV Subjects: Valve Implantation Procedure

The implantation of the Zephyr EBV valve was performed in eligible Zephyr EBV Subjects, either under general anesthesia on ventilators, or using conscious sedation with unassisted breathing. Antibiotic coverage was given before and after the procedure. The targeted lobe for Zephyr EBV Treatment was ascertained based on the HRCT Scoring Form prepared by the CRL; only one lobe was treated in each study subject. Zephyr EBV implantation was permitted at either the lobar, segmental or subsegmental level, with preference for the earliest generation airway, with an intent to achieve complete lobar exclusion. Staged procedures and bilateral valve placement were not permitted in the VENT Pivotal Trial. The success of lobar exclusion (Acute Technical Success) was determined via bronchoscopy at the conclusion of the procedure.

4.2.4 Zephyr EBV Subjects: Post Implantation Procedure

Subjects were recovered from the anesthesia per hospital protocol, and monitored by pulse oximetry during the first 24 hours post-procedure. Supplemental oxygen therapy was titrated to achieve 90% oxygen saturation prior to hospital discharge. Chest physiotherapy was used to clear mucus or air remaining behind the valve, as was coughing unless there was evidence of atelectasis. All subjects were given a standard course of prophylactic antibiotics and post-operative inhaled bronchodilators.

Any subject with radiographic evidence of atelectasis was kept in-hospital under observation for at least 2 days post procedure. A stable pneumothorax was an expected response to lobar atelectasis and was not treated unless it persisted. When a chest tube became necessary, it was continued until signs of air leak ceased, at which time it was removed.

4.2.5 Zephyr EBV Subjects: Valve Removal Procedure

When removal was necessary, Zephyr EBV valves were removed according to the Instructions for Use. This could occur at any time during the procedure or later during the follow-up interval as deemed necessary by the Investigator. Any subject with either

an increase in RV > 15% or an FEV_1 decrease of > 15% and an RV decrease of < 5% during the first 30 days of follow-up was recommended to be considered for a valve removal procedure. All subjects treated with the Zephyr EBV device, including those that underwent valve removal, were followed for the entire protocol-specified follow-up period.

4.2.6 All Study Subjects: Follow-up Procedures

Follow-up assessments were scheduled for all study subjects at 2 – 3 days, 1 week, 1, 3, and 6 months, and at 1year.

Spirometry was performed both pre and post bronchodilator treatment based on American Thoracic Society standards (1994).[20] Body plethysmography post bronchodilator treatment was performed according the American Association of Respiratory Care Clinical Practice Guideline (2001).[21] Diffusing capacity (DL_{CO}) was measured using the single-breath carbon monoxide method according to American Thoracic Society standards (1995).[22] Six-Minute Walk testing was performed according to American Thoracic Society standards (2002)[23]; dyspnea and overall fatigue was measured in all subjects using the Borg Scale prior to and immediately following performance of the 6MWT. Cycle ergometry to determine maximum workload was performed according to the protocol used in the NETT study[24] and with concurrent Borg scale testing. Supplemental oxygen requirements were self-reported by study subjects including conditions of usage, duration of use and flow rate.

Health related quality of life (QoL) measurement was performed at baseline, 6 months, and 1 year using several instruments, including the St. George's Respiratory Questionnaire (SGRQ), the Modified Medical Research Council survey (mMRC) and the Quality of Well Being Scale (QWB). The QWB and mMRC were also administered at the 1 month follow-up visit.

4.2.7 Adverse Events

Adverse events, Serious Adverse Events and Unanticipated Adverse Device Effects were assessed and reported using standard FDA definitions. Abnormal laboratory values were not reported as adverse events; however, any clinical consequence of the abnormality, or the cause of the abnormal values, was reported as an adverse event.

All adverse events (serious and non-serious) were recorded on the Adverse Event CRF. Serious Adverse Events and/or Unanticipated Adverse Device Effects were reported on the Serious and/or Unexpected Adverse Event CRF and the event was required to be reported by telephone or fax to the Adverse Events Coordinator within 24 hours after

learning of the event. Information regarding deaths was documented on the Serious and/or Unexpected Adverse Event and Report of Patient Death CRFs.

4.3 Study Management

4.3.1 Investigator Selection, Responsibility, Training and Performance

Emphasys Medical selected qualified Investigators based upon training and experience, and shipped devices only to participating Investigators. Each Investigator had fully executed clinical contracts; IRB approvals; signed /dated CVs on file and a signed statement attesting to the Investigators' agreement to conduct the study in accordance to the investigational plan, applicable Federal regulations and other specific conditions of approval as may have been imposed by the local governing IRB. Investigator financial disclosures and investigator certificates can be found in Appendix 7-4.

Study sites selected for this clinical study were determined to have a sufficient number of cases available to allow timely enrollment of subjects into this study. The Sponsor monitored the Investigators for evidence of noncompliance with the signed agreements, investigational plan, or conditions included in approvals imposed by an IRB and took necessary steps to ensure such compliance.

4.3.2 Monitoring and Source Documentation

Monitors qualified by training and experience were selected by the Sponsor to monitor the investigational study in accordance with applicable regulations. Emphasys Medical and/or its designee conducted Investigational Site monitoring to ensure that all Investigators were in compliance with the Investigational Plan, the Investigator Agreement, all applicable regulations, and any conditions of approval imposed by the reviewing IRB. Emphasys Medical and/or its designee monitored the sites to ensure the relevant data on completed Case Report Forms (CRFs) was substantiated by source documentation. While Emphasys Medical conducted a significant portion of this monitoring through its own full-time clinical research staff, these efforts were augmented as needed by utilizing two external contract research organizations (Bailer Research, Inc., Lake Hopatcong, NJ and ICRC Inc., Reno, NV).

Values entered on case report forms were compared against subject medical records and other associated source documents to ensure accuracy. For each such visit, monitors were required to sign a monitoring log kept at the site and also prepare a written report documenting their activities. Following each visit, monitors prepared a short summary letter or email to the site summarizing the visit and any action items identified.

Please refer to Appendix 7-5-4 for copies of blank Case Report Forms.

4.3.3 Data Transmittal and Record Retention

Data for the study was collected on 3-part case report forms (CRFs). Once monitored, the original copy of the 3-part form was sent to Sponsor's data management group for processing. Upon receipt, the CRF was logged into a tracking database which was used to determine overall CRF collection status for the study. All received CRFs were filed in locked, fireproof filing cabinets.

4.3.4 Managing Study Deviations

Any noted deviations from the protocol that occurred during the course of the study site were fully documented using a Protocol Deviation Form. Blank copies of these forms were included with each set of subject CRFs. Once completed, these forms were collected and processed in the same manner as all other CRFs.

4.3.5 CEC Adverse Event Adjudication

Over the course of the clinical investigation, the CEC reviewed and adjudicated 1,437 reported events. Some site-reported events were combined into a single coded event to more accurately reflect the clinical course of the event and to eliminate potential double counting of events. Some site-reported events that appeared to be unrelated to the subject's pulmonary status and/or participation in the clinical trial were also removed from data analysis sets presented in Section 9 - Safety Outcomes. The CEC pursued a uniform approach to these designations independent of subject assignment. A listing of site reported events that were either combined and/or removed can be found in Appendix 7-5-11.

4.4 Data Management

4.4.1 Data Screening and Acceptance

Upon receipt by the Sponsor, all CRFs were visually reviewed for completeness and legibility. Any issues noted were queried by Sponsor. This involved completing a 3 part Correction/Query form (CQ form) which would describe the CRF page impacted and briefly describe the finding. A separate column on the form provided room for the site to respond to the query. Working copies of these forms were kept by Sponsor while the original and a site copy were forwarded to the study site. The site would then complete and sign the form and send the original back to Sponsor. Each query was filed on top of the CRF to which it pertains.

4.4.2 Data Processing and Quality Control

CRF data were manually entered into a central, controlled study database. Edit checks were performed to identify possible discrepancies, including for blank fields, statistical

outliers and date and unit inconsistencies. Each suspect data field identified by this process was corrected by reference to the original CRF. For issues that could not be resolved by reviewing in-house documentation, a Correction/Query form was completed and sent to the site. These processes continued repeatedly until all queries were resolved.

A random sample of 10% of subjects entered into the database had their CRFs audited. Every data field on every CRF for each of these subjects was reviewed against the data in the database. An acceptance criteria error rate of 0.5% (i.e. 1 in 200) was established. The observed error rate was well below this threshold.

4.4.3 Confidentiality and Protection of Study Files

All CRFs and associated documents identified subjects only by an alphanumeric code. Any subject name information received from study sites was immediately removed or blacked out and substituted with the subject identifier code. All CRFs and study related documents were organized by site and subject and stored in locked, fireproof filing cabinets.

4.5 Statistical Analysis Plan

The complete Statistical Analysis Plan is included in Appendix 7-5-7 and is summarized in this section.

4.5.1 Sample Size

The null hypothesis and alternative hypothesis are presented below where ΔFEV_1 equals the mean percent improvement response in FEV_1 from baseline for each group at 6 months.

$$H_0: \Delta\, FEV_1(EBV) - \Delta\, FEV_1\,(Control) = 0\%$$

$$H_A: \Delta\, FEV_1(EBV) - \Delta\, FEV_1\,(Control) \neq 0\%$$

The sample size was estimated to detect a 15% difference between the study arms for the mean change of FEV_1 and a 17% change of 6MWT from baseline to 6 months.

A 2:1 treatment allocation favoring Zephyr EBV versus Control was utilized. Based on an estimated 0.41 correlation between the 6MWT and FEV_1, and expected loss rate of 10%, 270 subjects were required to achieve a minimum of 246 subjects (164 EBV, 82 Controls). A two-tailed 5% Type I error was used with 80% overall power.

4.5.2 Error and Bias Control

A variety of proven means of minimizing error and bias in clinical studies were utilized in the VENT Pivotal Trial. Study subjects were qualified for study participation under

explicit inclusion and exclusion criteria. Study subjects were randomized to study arms. All study subjects were treated in accordance with well-defined study procedures, administered and recorded consistently across all study sites by appropriately trained and skilled study staff. Study progress and protocol compliance were overseen by an Operations Committee. Concurrent assessment of safety outcomes, subject welfare and scientific adequacy of the study was maintained by a DSMB. Outcome events were adjudicated by an independent CEC. Regular site monitoring and data quality standards were maintained throughout the study.

4.5.3 Analytic Methods

The analysis populations include the multiple-imputation intent-to-treat (ITT), modified intent-to-treat (mITT), and completed cases (CC).

- The ITT population was defined as all randomized subjects analyzed by the groups to which they were randomly assigned, regardless of the actual treatment received. Consented subjects who withdrew consent prior to randomization, or who were found not to meet the inclusion/exclusion criteria prior to randomization, were recorded on a screening log at each clinical site and were not included in the intent-to-treat group. Missing data was multiply-imputed and the results combined for analysis.
- The mITT population was defined as all randomized subjects who received study-directed treatment and had any follow-up visits.
- The CC population was defined as all randomized subjects who received study directed treatment and who had 180-day observations within a window of 150 – 225 days.

The primary effectiveness outcome measures and secondary effectiveness outcome measures were analyzed using the multiple-imputation ITT population. Confirmatory and additional effectiveness analyses were performed using the CC population.

Safety analyses were performed using the mITT population. For the safety analysis, the time was determined by subtracting the randomization date from the event date except for a limited number of subjects whose follow-up schedule had been re-set by the site due to illness or lack of available product. For those subjects, the procedure date was subtracted from the event date.

4.5.4 Baseline, Demographic and Procedural Data

Study subjects were comprehensively evaluated for baseline characteristics, including demographic information, pulmonary medications, medical history, supplemental oxygen

use, lung function, arterial blood gases, exercise tolerance and Borg test results. Zephyr EBV Subjects had data gathered regarding the length of procedure time, target lobes, anesthesia and airway management, use of rigid bronchoscopes, number of valves implanted, Acute Technical Success, valve removal and device malfunctions.

4.5.5 Safety Measures and Outcomes

The primary safety outcome measure for the VENT Pivotal Trial was the Major Complications Composite (MCC). An MCC outcome event occurred when a study subject had one or more of the component events listed in the following table.

Table 1 Major Complications Composite

Death, all-cause
Empyema
Massive hemoptysis resulting in respiratory failure or blood loss > 300cc in $\leq$24hr
Pneumonia distal to the implanted valves
Pneumothorax or prolonged air leak > 7 days
Respiratory failure on mechanical ventilation for > 24 hours

Source: Appendix 7-5-2, Protocol.

The Primary Safety Outcome for the VENT Pivotal Trial was the proportion of subjects in each group with one or more MCCs through 6 months of follow-up, reported with exact 95% confidence intervals. MCCs were further evaluated by Cox regression, by time period through one year, and by valve removal status through one year.

Additional prospectively determined safety outcome measures were:

1. Complications (adverse events and serious adverse events through one year)
2. Device-related and procedure-related AEs during procedure hospitalization
3. Device-related and procedure-related AEs following procedure hospitalization
4. All-cause mortality
5. Rehospitalization

4.5.6 Effectiveness Measures and Outcomes

The two primary effectiveness outcome measures for this study were:

1. Mean percent change in FEV_1 at 6 months
2. Mean percent change in 6MWT at 6 months

The Primary Effectiveness Outcome for the VENT Pivotal Trial was the multiple-imputation, intent-to-treat comparison of the percent change in each of the two outcome measures (FEV_1 and 6MWT) as measured at 180 days compared between Control Subjects and Zephyr EBV Subjects. Both FEV_1 and 6MWT results need to be statistically-significantly different for the Primary Effectiveness Outcome to be met.

The secondary effectiveness outcome measures for this study were:

1. Change in St. George's Respiratory Questionnaire (SGRQ) score from baseline
2. Change in Modified Medical Research Council (mMRC) Dyspnea Scale from baseline
3. Change in maximum workload (watts) as measured by cycle ergometry from baseline
4. Change in supplemental oxygen requirement (liters / day) from baseline

The four Secondary Effectiveness Outcomes for the VENT Pivotal Trial were these four outcome measures as measured at 180 days compared between Control Subjects and Zephyr EBV Subjects in the same multiple-imputation, intent-to-treat manner as the Primary Effectiveness Outcome.

Additional pre-specified effectiveness outcome measures for this study were:

1. Percent change in RV from baseline
2. Percent change in DL_{CO} from baseline
3. Change in Quality of Well Being Scale from baseline
4. Change in BODE Index from baseline
5. Technical Success (Zephyr EBV only)

Pre-specified responder analyses regarding the clinical importance of the observed treatment responses were the following:

1. Subjects with Major Improvement ($\geq$ 15%) in FEV_1
2. Subjects with Major Improvement ($\geq$ 15%) in 6MWT
3. Subjects with Any Improvement ($\geq$ 0%) in FEV_1
4. Subjects with Any Improvement ($\geq$ 0%) in 6MWT

Pre-specified, analysis-plan-generated subgroup analyses were the following:

1. High Heterogeneity
2. Technical Success (Complete Lobar Exclusion)
3. Complete Fissure Integrity

Additional *post hoc* responder analyses were performed in response to FDA inquiries regarding the clinical importance of the treatment responses:

1. Subjects with $\geq$ 8 point improvement in SGRQ
2. Subjects with $\geq$ 1 point improvement in mMRC
3. Subjects with $\geq$ 10 watt improvement in maximum workload during cycle ergometry
4. Subjects with $\geq$ 1 point improvement in the BODE Index

An investigation of Zephyr EBV treatment, target lobe volume reduction (TLVR) as measured by HRCT and treatment effect as measured by FEV_1 was performed to see if

significant and relevant predictors could be determined for the hypothesized mechanism of action.

Additional *post hoc* assessments of primary and secondary outcome measures using available one year data were performed in response to an FDA request regarding durability of the treatment response.

4.6 Imaging Procedures

Study imaging procedures are fully described in Appendix 7-1, VENT – General CT Manual of Procedures (MOP). High resolution computed tomography (HRCT) images were utilized for the following purposes in the conduct of the trial and subsequent assessment of the results:

1. Subject eligibility screening – Disease severity and distribution at baseline
2. Treatment targeting – Disease distribution at baseline
3. Assessment of baseline predictors of success – Inter-lobar collateral flow proxy (fissure integrity), disease severity, disease heterogeneity, target lobe ventilation (volume change from TLC to RV)
4. Volume reduction assessment – Target lobe volume change from baseline to 180 day follow-up
    a. Quantify effect of treatment
    b. Correlation with outcomes measures to assess volume-reduction mechanism of action
5. Assessment of technical success – Determination of complete lobar exclusion (technical success) at follow-up and the effect of complete lobar exclusion on outcomes

The collection and analysis of high resolution computed tomography (HRCT) images were coordinated by an HRCT Core Lab (MedQia, in association with the David Geffen School of Medicine at UCLA). The process consisted of five general steps:

4.6.1 Image Acquisition

Each investigational site was provided with an imaging Manual of Procedures (MOP) tailored specifically for the type of scanner in use at that site. This manual specified certain scanner and image reconstruction settings necessary to ensure the image would be analyzable by the automated quantitative image analysis software used to assess disease distribution and severity as well as volume distribution by lobe. These specifications also ensured that the baseline and follow-up CTs were captured under identical conditions

In addition, the manual included a section on how to educate and instruct subjects about their breathing during the image acquisition to minimize motion artifacts and also ensure maximal consistency between baseline and follow-up scans.

Full thoracic HRCT images of each subject were captured at two points in the breathing cycle. The first was at maximal inspiration (Total Lung Capacity – TLC), the other was at maximal expiration (Residual Volume – RV).

4.6.2 Quality Control

The imaging Manual of Operations also outlined specific requirements for scan quality control. Sites were required to submit images of phantoms (water-containing test fixtures) which were then assessed by the HRCT Core Lab for appropriate quality and image capture settings.

4.6.3 Quantitative Image Analysis

All study subjects were scheduled for four HRCT scans during the course of the study:

- Baseline at TLC (full inspiration)
- Baseline at RV (full exhalation)
- Day 180 at TLC (full inspiration)
- Day 180 at RV (full exhalation)

Baseline HRCT images were analyzed quantitatively using automated software which used edge detection algorithms and other processing techniques to automatically define that portion of the HRCT corresponding to lung tissue. The software calculated the proportion of image voxels that fell below a pre-defined Hounsfield unit threshold (i.e. a certain grey-scale level) which correlates to the degree of emphysematous lung destruction. Follow-up scans were analyzed in an identical manner. Both the full-inspiration and full-expiration scans were analyzed for volume and Density Score by lobe.

4.6.4 Density (Emphysema) and Heterogeneity Scoring

Density (or Emphysema) Score: The percentage of each lung lobe volume below the pre-defined Hounsfield threshold was then reported as the Density Score in % for that lobe. For example, a Density Score of 75% meant that 75% of the volume in that lobe met the Hounsfield threshold and was considered destroyed by emphysema.[*] These metrics were calculated for each lobe separately, using both the full-inspiration and full-expiration scans. The Density Scores from the full-inspiration scan were used by the HRCT Core

[*] For the purposes of determining inclusion criteria, the Density Score was converted into integer scores as follows: 0% = 0, 1 – 25% = 1, 26 – 50% =2, 51 – 75% = 3 and > 75% = 4.

Lab to determine subject eligibility and target lobe per the algorithm defined in the protocol.

Heterogeneity Score: The difference between the Density Scores of the target lobe and the ipsilateral non-target lobe (in %) was the Heterogeneity Score for that subject.*

4.6.5 Fissure Integrity Assessment

In addition to quantitative assessment of each HRCT, a manual reading of fissure integrity was also conducted in the target lung of each subject using the baseline HRCT full-inspiration image. Each fissure in the lung was graded by trained radiologists using a three point scale: complete, incomplete or absent.† The HRCT image below shows an example of a complete fissure in the right lung and an incomplete fissure in the left lung. A fissure must be complete in all views in order to be assigned "Complete".

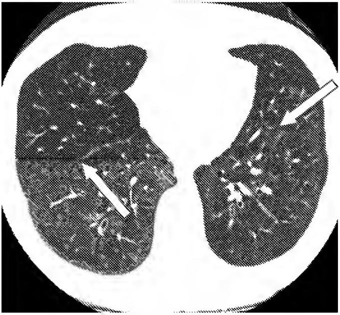


Figure 5 Fissure Integrity Example

4.6.6 Lobar Exclusion Assessment

The 180 day follow-up HRCT for each Zephyr EBV Subject was also read manually to determine whether all airways leading to the target lobe were effectively blocked with valves. If the radiologist determined that the lobe was not fully blocked, the reason for technical failure was noted (e.g. open side branch).

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* For the purposes of determining inclusion criteria, the Heterogeneity Score was converted into the difference between the upper lobe Density Score and the lower lobe Density Score; if the difference was ≥ 1, the patient was eligible.

† The actual results were binary: either complete or incomplete.

4.6.7 Target Lobe Atelectasis Score (TLAS) Methodology

The HRCT Core Lab calculated volumes by lobe at each of the four scans. The Target Lobe Atelectasis Score (TLAS), calculated both at RV ("$TLAS_{RV}$") and at TLC ("$TLAS_{TLC}$"), was determined for that lobe by the following formula:

$$TLAS = \frac{(Volume_{Day180} - Volume_{Baseline})}{Volume_{Baseline}}$$

The resulting value—expressed either as a percent or a decimal—indicates progressive volume loss up to a hypothetical complete atelectasis (−100% or −1.00). Therefore, the TLAS is a measure of Target Lobe Volume Reduction (TLVR) over 6 months of study follow-up. TLAS was calculated at Residual Volume ($TLAS_{RV}$) and at Total Lung Capacity ($TLAS_{TLC}$). Study analyses were performed using $TLAS_{TLC}$.

4.7 Changes in the Conduct of the Study

4.7.1 Protocol Amendments

The first study subjects were enrolled under Emphasys Medical IDE Protocol version 630-0001-J dated October 22, 2004. There were no changes to the protocol during enrollment and follow-up phases of the study.

4.7.2 Changes in the Statistical Analysis Plan

The original statistical analysis plan (SAP) was found in Appendix H of IDE Protocol version 630-0001-J dated October 22, 2004. Subsequent to this, three revisions of the SAP were submitted to and ultimately approved by the Agency as IDE supplements. These revisions were dated July 11, 2005, November 7, 2006, and April 12, 2007.

The July 11, 2005 revision was originally proposed in an IDE supplement April 12, 2005. This revision clarified that the primary analyses between Zephyr EBV Subjects and Control Subjects would be one-sided tests of superiority, replaced GEE modeling with GLM modeling for multivariate analysis, and added a per-subject analysis of the proportion of subjects with any increase from baseline at 6 months for FEV_1 and 6MWT.

The November 7, 2006 revision was originally proposed in an IDE supplement dated June 16, 2006. This revision clarified and defined potential covariates and better defined analysis plans for the covariates, changed the method of determining successful lobar exclusion based on improved HRCT Core Lab capability, divided adverse event time courses into three categories, and added reduction of oxygen consumption to a secondary analysis of clinical success.

The April 12, 2007 revision was originally proposed in an IDE supplement dated April 12, 2007. This revision clarified the abbreviated analyses to be completed for study subjects that were enrolled under IDE Protocol version 630-0001-I. These subjects are not part of this clinical study report.

These changes did not affect the validity of the data or information resulting from the completion of the approved Protocol, the relationship of likely subject risk to benefit relied upon to approve the Protocol, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the human subjects involved in the investigation.

Please refer to Appendix 7-5-3 for the full text of prior Statistical Analysis Plans.

4.7.3 Additional Analyses Resulting from FDA Communications

Communications with the FDA during the review of the premarket application resulted in additional *post hoc* analyses being included in the Clinical Study Report. These further analyses included justification of the clinical significance of treatment effect (additional responder analyses of outcome measures), and extended data on performance (available primary and secondary effectiveness outcome measures through 12 months).

4.7.4 Changes in the Experimental Devices

At the beginning of the enrollment period, only the Zephyr 4.0 EBV was available for clinical use to treat bronchial lumens ranging in diameter from 4.0 mm to 7.0 mm. In an IDE supplement dated February 10, 2005, the Zephyr 5.5 EBV was submitted for approval to treat lumens from 5.5 mm to 8.5 mm. This was approved by the Agency on March 31, 2005 (G020230/S30 & S31). The molding process for the one-way valve component of the Zephyr 4.0 EBV was modified during the course of trial and discussed in a Notice of IDE Change dated August 15, 2005. Based on Agency input, the Statistical Analysis Plan was updated to analyze the potential impact of valve size and/or valve version on clinical results. All subsequent multivariate models included valve size and valve version.

During the clinical evaluation, 32 Zephyr 5.5 EBV devices were withdrawn because of the potential to create a loose monofilament fragment during device loading using an earlier version of the loading system. The withdrawal was documented in an IDE supplement dated September 12, 2005. Loading system improvements to prevent the recurrence of fragments was documented in a Notice of IDE Change dated March 30, 2006.

4.8 Protocol Deviations

A total of 2,492 protocol deviations of any kind were observed during the conduct of this clinical investigation. These occurred in several categories, including visits or tests occurring outside of scheduled windows, missed subject visits, the performance of telephone follow-up instead of a clinic visit, failure to perform protocol required testing, enrollment of subjects who did not meet eligibility criteria, pulmonary rehabilitation procedures that did not meet protocol requirements, medication use that was noncompliant with the protocol, failure to obtain written informed consent prior to study procedures, and irregularities in performing specified pulmonary function testing.

The majority of these resulted from a Sponsor-initiated remonitoring effort undertaken to ensure lung function tests were being gathered and reported in the standardized manner prescribed by the study protocol. Although this effort generated a large number of minor deviations, the primary outcomes were impacted infrequently, were not significantly different between the two treatment groups and resulted in no significant impact on the scientific integrity of the outcome data.

A total of 99 eligibility criteria deviations occurred. A total of 62 subjects did not meet the inclusion / exclusion criteria at either a screening visit and/or at baseline, excluding subjects whose eligibility was not known at time of Screen 2 or Baseline but were late confirmed to meet the eligibility criteria. In 23 of these (37.1%), criteria that were not met at the screen 2 visit were subsequently met at the baseline visit.. In those cases where eligibility criteria were violated, the magnitude of difference in the observed metric compared to the protocol defined threshold was generally small. The study population enrolled is therefore expected to be consistent with that defined by the study protocol.

A line listing of all protocol deviations is presented in Appendix 7-5-6 and deviations are summarized by categories in the following table. A detailed listing of the 62 subjects that that did not meet inclusion / exclusion criteria at either a screening visit and/or at baseline is presented in Amended Statistical Analysis Report: Section 21.3.

Table 2 Summary of Protocol Deviations

Category (per CRF)				Total #	% of Total
1	Subject contact outside of protocol required window			222	9%
2	Test / procedure done outside of protocol required window			133	5%
3	Missed subject contact			96	4%
4	Subject contact by telephone (office visit required)			24	1%
5	Protocol required test not done			384	15%
6	Subject did not meet eligibility criteria			99	4%
7	PR Program does not meet protocol requirements			35	1%
8	Medication not in compliance with protocol			11	< 1%
9	Written informed consent not obtained prior to procedure			1	< 1%
10	PFT related deviations	Plethysmography	Reproducibility of measurements	256	10%
			# Maneuvers measured	88	4%
		Spirometry	Reproducibility of measurements	140	6%
			# Maneuvers measured	150	6%
		Exercise Tolerance	Cycle Ergometry Ramp Rate	97	4%
			Cycle Ergometry Supplemental O2	38	2%
			6MWT Supplemental O2 variation	69	3%
		Diffusing Capacity	# Maneuvers measured	35	1%
			Reproducibility of measurements	8	< 1%
		Multiple PFT Deviations	Cycle Ergometry and 6MWT	1	< 1%
			PFT Maneuvers	181	7%
			PFT Reproducibility	169	7%
			PFT Reproducibility & Maneuvers	199	8%
			PFTs & Exercise Tolerance & 6MWT	4	< 1%
			PFTs & Exercise Tolerance and Cycle Ergometry	8	< 1%
			Other combinations	6	< 1%
			Unknown	5	< 1%
		Other	EBV Procedure-related	10	< 1%
			Other Protocol Deviation	12	< 1%
			VQ Scan Percentages	8	< 1%
			ABGs O2 Supplementation	3	< 1%
Total				**2,492**	**100%**

Source: P070025, September 21, 2007, Volume 011, Page 57

4.9 Study Definitions

In this Clinical Study Report, the following terms have the specific meanings as defined below.

1. 95 Percent Confidence Interval (95% CI): An estimated range of values which is likely to include 95% of all randomly selected values from the population. The estimated range is based on the assumption that that population is normally distributed.

2. Acute Technical Success: Complete exclusion of the target lobe determined via bronchoscopy at the conclusion of the procedure. (See Technical Success)
3. Adverse Event (AE): An Adverse Event is any complication whether considered major or minor and whether or not associated directly with the Emphasys Endobronchial Valve procedure.
4. BODE: A composite index of pulmonary disease state which includes the BMI, Airflow Obstruction, Dyspnea and Exercise Capacity index.
5. Body Mass Index (BMI): An index of body weight normalized by height, calculated as (weight [kg] / height [m]^2).
6. Borg test: A questionnaire rating perceived exertion.
7. Carina – The ridge at the origin of an airway bifurcation. Denotes the most-proximal point of an airway branch.
8. Case Report Form (CRF): Form completed by sites to record all study related subject data.
9. Chest X-Ray (CXR): A diagnostic test that uses electromagnetic energy beams to produce images of the internal tissues, bones, and organs of the thorax onto film.
10. Chronic Obstructive Pulmonary Disease (COPD): A lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible– encompasses emphysema and chronic bronchitis.
11. Clinical Events Committee (CEC): Committee of Pulmonologists and Thoracic Surgeons not participating in the study who met regularly to review and adjudicate all Adverse Events.
12. Clinical Study Report (CSR): A report summarizing the results of the VENT clinical study.
13. Code of Federal Regulations (CFR): A compilation of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government of the United States of America.
14. Completed Case (CC): All randomized and eligible subjects who received study-directed treatment and who had 6 months of follow-up.
15. Computer Tomography (CT): Medical imaging technique using tomography to generate three dimensional images of the scanned body part.
16. Confidence Interval (CI): Gives an estimated range of values which is likely to include an unknown population parameter, the estimated range being calculated from a given set of sample data.
17. Core Radiology Lab (CRL): Lab at the University of California Los Angeles responsible for implementing standardized HRCT image collection at each site, and performing quantitative image analysis of screening HRCT scans to determine subject eligibility.

18. Corrections/Query Form (CQ): Form sent to sites to document and resolve completeness, legibility and other issues with case report forms.
19. Cycle ergometry: Stationary cycling used to measure the amount of work a subject can perform.
20. Data Safety Monitoring Board (DSMB): Committee consisting of a statistician and specialty physicians responsible for making recommendations to the Operations Committee regarding outcome analysis and any potential situations in which patient safety, patient welfare, or the scientific adequacy of the study were at risk.
21. Density Score (DS): The proportion (in %) of lobar lung parenchyma destroyed by emphysema as established by HRCT. A synonym for Emphysema Score (in %).
22. Destruction score: The sum of the upper lobe and lower lobe integer Emphysema Scores. See Protocol at Appendix 7-5-2, Section 6.7.5.
23. Diffusing Capacity (Lung) (DL_{CO}): A measure of the rate of carbon monoxide gas transfer across the alveolar-capillary blood-gas membrane.
24. Diffusing Capacity (Lung) % Predicted (DL_{CO} % predicted): A measure of DL_{CO} normalized for gender, age, and height.
25. Electrocardiogram (ECG): A diagnostic test which records the electrical activity of the heart over time.
26. Emphysema Score (ES): The proportion (in %) of lobar lung parenchyma destroyed by emphysema as established by HRCT. A synonym for Density Score.
27. Expiratory Reserve Volume (ERV): The volume of gas that can be voluntarily exhaled beyond the FRC and the RV.
28. FEV_1 / FVC: The calculated ratio of the FEV_1 and FVC.
29. Forced Expiratory Flow ($FEF_{25\text{-}75\%}$): The Forced Expiratory Flow is the average flow rate measured over the middle 50% of the exhaled volume.
30. Forced Expiratory Volume (FEV_1): The forced expiratory volume in one second is the volume of gas that can be forcefully exhaled in one second after a maximal inspiration.
31. Forced Expiratory Volume Percent Predicted (FEV_1 % predicted): A measure of FEV_1 normalized for race, gender, age, and height.
32. Forced Vital Capacity (FVC): The total volume of gas exhaled during a forced exhalation after a maximal inspiration.
33. Forced Vital Capacity Percent Predicted (FVC % Predicted): FVC normalized for race, gender, age, and height.
34. Fraction of Inspired Oxygen (FiO_2): Percentage of oxygen contained in inspired air.

35. Functional Residual Capacity (FRC): The volume of air present in the lungs at the end of passive expiration.
36. Good Clinical Practice (GCP): An international quality standard that is provided by the International Conference on Harmonisation (ICH). GCP guidelines include protection of human rights as a subject in clinical trial as well as providing standards on how clinical trials should be conducted, and defines the roles and responsibilities of clinical trial sponsors, clinical research investigators, and monitors.
37. Heart failure: A new diagnosis of heart failure or an increase in NYHA functional classification score status of 1 or more.
38. Heterogeneity score (HS): The difference (in %) between ipsilateral lobe Density Scores.
39. Heterogeneity: Degree of non-uniform distribution of diseased, emphysematous areas in the lung.
40. High-Resolution Computed Tomography (HRCT): Computed tomography with narrow collimation to reduce volume-averaging and an edge-enhancing reconstruction algorithm to sharpen the image.
41. Homogeneity: Degree of uniformity in the distribution of diseased.
42. HRCT Density Score: A computer-automated grading of the percent emphysematous destruction on a lobar level by HRCT.
43. Hypoxemia: Increased oxygen requirement (> 24 hour hours post-procedure) to maintain oxygen saturation >90% where increased oxygen requirement is defined as either:
    a. > 1.5 liter/min increase over baseline if by nasal cannula.
    b. > 10% increase in FiO_2 over baseline if by mask.
44. Imputation: Random assignment of values for missing data in the Intent-to-Treat population. Imputation is performed multiple times (Multiple Imputation) in order to ensure that results are not due to chance.
45. Inspiratory Capacity (IC): The maximum volume of air that can be inspired after reaching the end of a normal, quiet expiration.
46. Institutional Review Board (IRB): A committee of physicians, statisticians, researchers, community advocates, and others that ensures that the design and conduct of a clinical trial is ethical and that the rights of study participants are protected.
47. Intent-to-Treat (ITT): All randomized subjects analyzed by the groups to which they were randomly assigned, regardless of the actual treatment received. ITT1 is the first of multiple imputation populations, ITT2, is the second, etc.

48. Ipsilateral Lung, Non-target Lobe Volume – The volume of the remaining, non-targeted lobe(s) of the target lung as determined by the Radiology Core Lab computer analysis.
49. Left Ventricular Ejection Fraction (LVEF): A measure of how much blood the left ventricle of the heart pumps out with each contraction.
50. Lobar Exclusion (6 Months): Core Radiology Lab confirmation that all airways feeding the Target Lobe have been completely blocked by a valve(s), with no detectable leaks around the periphery of the valve.
51. Lobar Exclusion (Acute): Bronchoscopic confirmation that all airways feeding the Target Lobe have been blocked with a valve.
52. Lost To Follow Up (LTFU): Study subject who does not return for protocol required follow-up visits.
53. Lung Volume Reduction Surgery (LVRS): Surgical treatment for advanced emphysema where the most diseased portions of the lungs are removed with the goal of improving lung function.
54. Major Complications Composite (MCCs):

Death, all-cause
Empyema
Massive hemoptysis resulting in respiratory failure or blood loss >300cc in $\leq$24hr
Pneumonia distal to the implanted valves
Pneumothorax or prolonged air leak > 7 days
Respiratory failure on mechanical ventilation for >24 hours

55. Major Complications Composite (MCC): The primary safety outcome for VENT. A per-subject assessment of Major Complications from day 0 to 180.
56. Maximum Voluntary Ventilation (MVV): The greatest volume of gas that can be breathed per minute by voluntary effort.
57. Modified Medical Research Council Dyspnea Scale (mMRC): A scale from 0 to 4, which a subject utilizes to grade their breathlessness.
58. Multiple Imputation: Statistical method of replacing missing data with plausible values by multiple simulated versions. Each simulated dataset is analyzed by standard methods and the results are combined to produce estimates and confidence intervals that incorporate missing-data uncertainty.
59. Myocardial Infarction (MI): Destruction of heart tissue resulting from obstruction of the blood supply to the heart muscle.
60. National Emphysema Treatment Trial (NETT): A multi-center clinical trial supported by the National Heart, Lung, and Blood Institute (NHLBI) and the Center for Medicare and Medicaid Services (CMS) to study bilateral lung volume reduction surgery.

61. Operations Committee: Committee responsible for the day-to-day administrative management of the trial.
62. Outcome: a specifically defined outcome measure recorded for a study subject at a specified time. Often defined as primary or secondary outcomes, and used in assessing statistical hypotheses.
63. Outcome Measure: a specifically defined observation variable recorded for a subject at various time points after enrollment for the purpose of the ongoing assessment of the effect of a study treatment
64. Oxygen Saturation (SAT): The percentage that arterial blood is saturated with oxygen.
65. Peak Expiratory Flow Rate (P_{EFR}): The maximum flow rate achieved during a forced exhalation.
66. Peak Inspiratory Flow Rate (P_{IFR}): The maximum flow rate achieved during a forced inhalation.
67. Plethysmography: A method of calculating lung volumes by placing the subject in a closed system and measuring pressure and volume changes within the system.
68. Premature Ventricular Contraction (PVC): Premature heartbeats originating from the ventricles of the heart.
69. Pulmonary embolism: Occlusion of one or more pulmonary arteries by emboli as evidenced by a high probability VQ scan evidence of segmental or larger perfusion defects or direct anatomic evidence of pulmonary embolism by other means (e.g. CT, echo or other).
70. Pulmonary Function Testing (PFT): Various tests designed to measure the function of the lungs including FEV_1 and FVC.
71. Quality of Life (QoL): Subjective well-being assessed by either disease-specific or general QoL questionnaires.
72. Quality of Well Being Scale (QWB): A standardized, general quality of life assessment tool.
73. Residual Volume (RV): The volume of undissolved gas contained in the lungs at the end of maximal exhalation.
74. Sepsis: Systemic inflammatory response syndrome (SIRS) with proven microbial etiology established by positive blood culture, where SIRS is defined as subject having two or more of the following conditions:
    a. fever (oral temperature > 38° C) or hypothermia (< 36° C);
    b. tachypnea (> 24 breaths / min);
    c. tachycardia (heart rate > 90 beats / min);
    d. leukocytosis (> 12,000 / µL), leukopenia (< 4,000 / µL), or > 10% bands
75. Serious Adverse Event (SAE): A category of adverse events that are deemed to be serious by the clinical events committee (CEC).

76. Six Minute Walk Test (6MWT): A cardiopulmonary function test that measures a subject's exercise capacity by the distance in meters that he / she can walk in six minutes.
77. Spirometry: Lung function testing involving the assessment of inhaled and exhaled gas volumes.
78. Standard Deviation (SD): A statistical analysis that is the measure of the spread of values in a group.
79. St. George's Respiratory Questionnaire (SGRQ): A standardized quality of life measurement used to assess subjects with obstructive pulmonary diseases.
80. Supraventricular Tachycardia (SVT): A regular, abnormally fast heart beat (tachycardia) caused by rapid firing of electrical impulses from a focus above the atrioventricular node (A-V node) in the heart.
81. Target Lobe: The lung lobe that was to be treated as determined by the Study Protocol at Section 7.8.2 Treatment Targeting.
82. Target Lobe Atelectasis Score at Residual Volume ($TLAS_{RV}$): The change in target lobe volume determined by computer analysis of the changes in the HRCT scans performed at residual volume and recorded at baseline and 6 months post-procedure. $TLAS_{RV}$ is calculated with the following formula:

    $$TLAS = \frac{\left(Volume_{Day180} - Volume_{Baseline}\right)}{Volume_{Baseline}}$$

    The resulting value—expressed either as a percent or a decimal—indicates progressive volume loss up to a hypothetical complete atelectasis (−100% or −1.00). Therefore, the TLAS is a relative measure of target lobe volume reduction over 6 months of study follow-up.
83. Target Lobe Atelectasis Score at Total Lung Capacity ($TLAS_{TLC}$): Calculated in the same way as $TLAS_{RV}$ except it is calculated at total lung capacity instead of residual volume.
84. Target Lobe Volume: The volume of the target lobe determined by the Radiology Core Lab computer analysis.
85. Technical Success: Complete target lobe exclusion in Treatment subjects as confirmed by HRCT scan at 6 months. (See Acute Technical Success)
86. Total Lung Capacity (TLC): The volume of undissolved gas contained in the lungs at the end of maximal inhalation.
87. Total Lung Capacity % Predicted (TLC % predicted): Total Lung Capacity normalized for gender, age, and height.
88. Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in

nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

89. Vital Capacity (VC): The difference in volume from maximum inhalation (TLC) to maximum exhalation (RV).
90. Volume of Thoracic Gas (VTG): The volume of gas in the thorax whether in communication with patent airways or trapped in any compartment of the thorax. Usually measured at the end-expiratory level and is then equal to Functional Residual Capacity (FRC).
91. VQ scan: A diagnostic test of the lungs that compares inhaled gas distribution with infused blood perfusion.
92. Zephyr Endobronchial Valve (Zephyr EBV): Implanted device that is the subject of this PMA application.

5.0 STUDY ACCOUNTABILITY AND POPULATION

5.1 Investigators and Site Enrollment

Thirty one (31) Investigators at 31 Investigative Sites enrolled a total of 321 study subjects between December 22, 2004 and April 27, 2006. A list of all participating Investigators and Sites is presented in Appendix 7-5-1. Enrollment into the Control and Zephyr EBV Groups is summarized by site in the table below.

Table 3 Subject Enrollment by Site

Site	Control	EBV	Total
001	4	9	13
002	5	11	16
003	2	6	8
004	4	7	11
005	7	15	22
007	8	16	24
008	0	2	2
009	1	6	7
010	5	10	15
011	0	3	3
012	1	6	7
013	1	1	2
014	8	15	23
015	3	6	9
016	0	1	1
017	1	4	5
018	8	18	26
019	2	5	7
020	1	2	3
021	9	14	23
022	3	8	11
023	4	9	13
024	3	6	9
025	2	2	4
026	4	6	10
027	3	7	10
028	3	8	11
029	5	9	14
030	2	5	7
032	1	0	1
034	1	3	4
Total	**101**	**220**	**321**

Source: Attachment 3, Amended Statistical Analysis Report, Table 5:1

Stratification by site and exercise capacity was successful in achieving a ration of 1:2 Control Subjects to Zephyr EBV Subjects in each of the 4 defined strata. (See Attachment 3, Amended Statistical Analysis Report, Table 5:1)

5.2 Subject Accountability

All 321 study subjects were enrolled according to protocol-defined procedures. Primary outcomes were to be assessed at 6 months of follow-up, with an extended safety assessment at 1 year.

For 101 Control Subjects through 6 months of follow-up, 8 subjects withdrew informed consent and none had died, leaving 93 subjects alive and potentially evaluable at 6 months, of whom 79 (84.9%) had an evaluable visit. By the time of the 12 month safety assessment, 9 subjects withdrew informed consent and 3 had died, leaving 89 subjects alive and evaluable of whom 76 (85.4%) had an evaluable visit. By 1 year of follow-up, 13 eligible subjects had not completed their final study visit, of whom 12 had been lost to follow-up.

Table 4 Cumulative Subject Accountability Table by Visit – Control Subjects

Control Subjects	1 Month Visit [1]	3 Month Visit [1]	6 Month Visit [1]	1 Year Visit [1]
Enrolled	**101**	**101**	**101**	**101**
Died [2]	0	0	0	3
Withdrawn [2]	6	7	8	9
Eligible at Visit [3]	**95**	**94**	**93**	**89**
Visit at Interval [4]	84 (88.4%)	75 (79.8%)	79 (84.9%)	76 (85.4%)
Visit in Window [4]	74 (77.9%)	46 (48.9%)	59 (63.4%)	70 (78.7%)
Visit in Extended Window [4, 5]	0 (0.0%)	0 (0.0%)	16 (17.2%)	5 (5.6%)
Visit Beyond Window [4]	10 (10.5%)	29 (30.9%)	4 (4.3%)	1 (1.1%)
No Visit [4]	11 (11.6%)	19 (20.2%)	14 (15.1%)	13 (14.6%)
Lost to follow-up [2]	8 (8.4%)	9 (9.6%)	10 (10.8%)	12 (13.5%)

[1] Protocol defined windows.
[2] Deaths, withdrawn subjects and lost to follow-up are cumulative.
[3] The number eligible is the number enrolled minus the number that died and the number that withdrew.
[4] The denominator is the number eligible at that visit.
[5] For the 180-day visit, the extended windows ranged from 150 - 225 days and for 365 days the extended window was from 305 - 425 days.
Source: Attachment 3, Amended Statistical Analysis Report, Table 3:1

For 220 Zephyr EBV Subjects through 6 months of follow-up, 9 subjects withdrew informed consent and 6 died, leaving 205 subjects alive and evaluable at 6 months, of whom 193 (94.1%) had an evaluable visit for 6 months. By the time of the 12 month safety assessment, 12 Zephyr EBV Subjects withdrew informed consent and 8 had died,

leaving 184 (92.0%) subjects alive and evaluable. By 1 year of follow-up, 16 eligible subjects had not completed their final study visit, of whom 14 had been lost to follow-up.

Table 5 Cumulative Subject Accountability Table by Visit – Zephyr EBV Subjects

Zephyr EBV Subjects	1 Month Visit [1]	3 Month Visit [1]	6 Month Visit [1]	1 Year Visit [1]
Enrolled	**220**	**220**	**220**	**220**
Died [2]	0	2	6	8
Withdrawn [2]	5	8	9	12
Eligible at Visit [3]	**215**	**210**	**205**	**200**
Visit at Interval [4]	191 (88.8%)	196 (93.3%)	193 (94.1%)	184 (92.0%)
Visit in Window [4]	120 (55.8%)	111 (52.9%)	135 (65.9%)	148 (74.0%)
Visit in Extended Window [4, 5]	0 (0.0%)	0 (0.0%)	37 (18.0%)	30 (15.0%)
Visit Beyond Window [4]	71 (33.0%)	85 (40.5%)	21 (10.2%)	6 (3.0%)
No Visit [4]	24 (11.2%)	14 (6.7%)	13 (5.9%)	16 (8.0%)
Lost to Follow-up [2]	5 (2.3%)	6 (2.9%)	9 (4.4%)	14 (7.0%)

[1] Protocol defined windows
[2] Deaths, withdrawn subjects and lost to follow-up are cumulative.
[3] The number eligible is the number enrolled minus the number that died and the number that withdrew.
[4] The denominator is the number eligible at that visit.
[5] For the 180-day visit, the extended windows ranged from 150 - 225 days and for 365 days the extended window was from 305 - 425 days.
Source: Attachment 3, Amended Statistical Analysis Report, Table 3:2

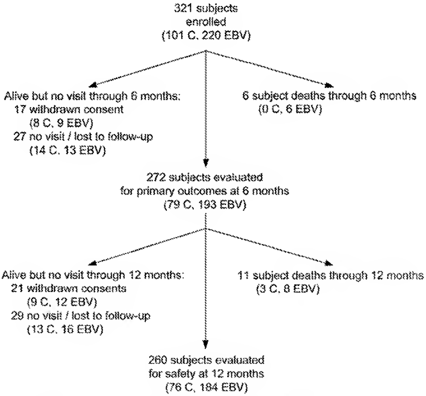


Figure 6 Subject Accountability Flow Chart

C = Control Subjects; EBV = Zephyr EBV Subjects
Source: Attachment 3, Amended Statistical Analysis Report Table 3:6

The following listing contains those Control Subjects who were discontinued due to death or withdrawn consent or who were lost to follow-up through study termination.

Table 6 Listing: Discontinued Control Subjects (Death, Withdrawal, LTFU)

Subject Code[3]	Randomization Date	Discontinuation Date	Days in Study[1]	Reason for Termination
	3/21/2006	3/10/2006	0[2]	Lost to follow-up
	11/7/2005	11/7/2005	0	Lost to follow-up
	9/12/2005	9/12/2005	0	Withdrew Consent
	8/18/2005	8/26/2005	8	Lost to follow-up
	9/14/2005	9/26/2005	12	Lost to follow-up
	4/7/2006	4/20/2006	13	Lost to follow-up
	9/14/2005	9/28/2005	14	Lost to follow-up
	7/20/2005	8/8/2005	19	Withdrew Consent
	3/25/2005	4/14/2005	20	Lost to follow-up
	8/25/2005	9/19/2005	25	Lost to follow-up
	9/16/2005	10/13/2005	27	Withdrew Consent
	3/31/2006	4/28/2006	28	Withdrew Consent
	8/11/2005	9/12/2005	32	Withdrew Consent
	7/11/2005	8/29/2005	49	Withdrew Consent
	7/21/2005	9/15/2005	56	Withdrew Consent
	5/31/2005	7/28/2005	58	Lost to follow-up
	8/8/2005	2/8/2006	184	Withdrew Consent
	4/11/2005	10/13/2005	185	Lost to follow-up
	6/29/2005	1/6/2006	191	Lost to follow-up
	3/9/2006	9/22/2006	197	Lost to follow-up
	6/27/2005	9/26/2005	207	Death
	4/7/2006	7/18/2006	212	Death
	5/2/2005	10/28/2005	230	Death
	4/8/2005	4/5/2006	362	Withdrew Consent

From randomization to last office visit
[2] Subject withdrew post-randomization, but prior to first office visit. Value of 0 was assigned.
[3] Subject ID has three components in the following order: site number, sequence number, and subject code. In Appendix 11, Completed CRFs for Deaths and Discontinuations, subjects are sorted based on site number and sequence number.
Source: Attachment 3, Amended Statistical Analysis Report, Table 3:4

The following listing contains those Zephyr EBV Subjects who were discontinued due to death or withdrawn consent or who were lost to follow-up through study termination.

Table 7 Listing: Discontinued Zephyr EBV Subjects (Death, Withdrawal, LTFU)

[3]	Randomization Date	Discontinuation Date	Days in Study[1]	Reason for Termination
	8/4/2005	8/1/2005	0[2]	Withdrew Consent
	3/27/2006	3/27/2006	0	Withdrew Consent
	6/9/2005	6/9/2005	0	Lost to follow-up
	8/17/2005	8/17/2005	0	Lost to follow-up
	9/16/2005	9/16/2005	0	Lost to follow-up
	11/13/2005	11/18/2005	5	Withdrew Consent
	7/20/2005	8/8/2005	19	Withdrew Consent
	1/24/2005	2/22/2005	29	Withdrew Consent
	7/15/2005	8/15/2005	31	Lost to follow-up
	9/16/2005	3/7/2006	38	Lost to follow-up
	3/31/2006	5/12/2005	38	Lost to follow-up
	1/19/2005	3/16/2005	56	Lost to follow-up
	8/18/2005	10/17/2005	60	Death
	4/15/2005	5/16/2005	66	Death
	3/29/2006	6/8/2006	71	Withdrew Consent
	8/12/2005	11/2/2005	82	Withdrew Consent
	4/19/2005	7/18/2005	90	Lost to follow-up
	6/17/2005	9/15/2005	90	Withdrew Consent
	3/4/2005	6/17/2005	105	Withdrew Consent
	3/2/2006	6/29/2006	119	Lost to follow-up
	2/16/2006	4/20/2006	133	Death
	1/28/2005	5/5/2005	148	Death
	4/13/2005	7/13/2005	154	Death
	4/4/2006	9/19/2006	168	Lost to follow-up
	4/25/2005	10/19/2005	177	Withdrew Consent
	6/13/2005	12/13/2005	183	Lost to follow-up
	10/7/2005	4/14/2006	189	Lost to follow-up
	3/2/2006	9/7/2006	189	Lost to follow-up
	6/23/2005	1/6/2006	197	Withdrew Consent
	12/1/2005	2/20/2006	210	Death
	4/8/2006	10/3/2006	238	Death
	4/12/2005	12/8/2005	240	Withdrew Consent
	11/29/2005	6/23/2006	293	Death
	9/26/2005	12/18/2006	448	Lost to follow-up

o last office visit

[2] Subject withdrew post-randomization, but prior to first office visit. Value of 0 was assigned.

[3] Subject ID has three components: site number, sequence number, and subject code. In Appendix 11, Completed CRFs for Deaths and Discontinuations, subjects are sorted based on site number and sequence number.

Source: Attachment 3, Amended Statistical Analysis Report, Table 3:5

Please refer to Appendix 11, Completed CRFs for Deaths and Discontinuations for completed case report forms for all discontinued subjects.

5.3 Device Accountability

A total of 2,618 Zephyr EBV devices, Zephyr EDC delivery catheters and Zephyr ELS loader systems were shipped to U.S. Investigational Sites as part of the VENT Pivotal Trial under the Investigational Device Exemption. Of the 2,618 individual components shipped, 1,539 were used or implanted in subjects, 995 were returned to Emphasys Medical, and 84 were used as training samples at the site or were opened and discarded. There were no unaccounted devices/components at the end of the clinical study.

Table 8 Device Accountability: VENT Pivotal Trial Investigational Devices

Device	Shipped	Implanted / Used	Returned	Sample / Destroyed	Unaccounted For Devices
Zephyr EBV	1,610	913	634	63	0
Zephyr EDC	689	423	253	13	0
Zephyr ELS	319	203	108	8	0
Total Devices	**2,618**	**1,539**	**995**	**84**	**0**

Source: P070025, September 21, 2007, Volume 011, Page 71

5.4 Imaging Accountability

All 321 subjects (100.0%) had a baseline HRCT evaluable for inclusion criteria. Of these 321 subjects originally enrolled, 280 were still in study follow-up as of the 6 month follow-up visit (Imaging Evaluable Subjects). Of these 280 Imaging Evaluable Subjects, 273 (97.5%) had a 6-month HRCT accepted by the Core Radiology Laboratory for protocol-specified imaging. HRCTs evaluable for fissure integrity at baseline were obtained in 93.8% of subjects, and paired baseline and 6-month images evaluable for lobar volume reduction at 6 months were obtained in 95.7% of subjects. HRCTs evaluable for valve position and lobar exclusion at 6 months were obtained in 98.5% of the Zephyr EBV Subjects.

Table 9 Imaging Accountability Table – Control Subjects

Imaging Accountability	Baseline	6 months
Subjects originally enrolled	101	101
Inadequate baseline HRCT	0	0
Death		0
Withdrawal		8
Lost to follow-up		10
Imaging evaluable subjects at interval	101	83
Core Radiology Lab HRCT imaging:		
Any HRCT	100.0% (101 / 101)	95.2% (79 / 83)
Evaluable for volume reduction % (n / N)		95.2% (79 / 83)
Evaluable for fissure completeness % (n / N)	92.1% (93 / 101)	

Source: Attachment 3, Amended Statistical Analysis Report, Table 4:1

Table 10 Imaging Accountability Table – Zephyr EBV Subjects

Imaging Accountability	Baseline	6 months
Subjects originally enrolled	220	220
Inadequate baseline HRCT	0	0
Death		5
Withdrawal		9
Lost to follow-up		9
Imaging evaluable subjects at interval	220	197
Core Radiology Lab HRCT imaging:		
Any HRCT	100.0% (220 / 220)	98.5% (194 / 197)
Evaluable for volume reduction % (n / N)		95.9% (189 / 197)
Evaluable for fissure completeness % (n / N)	94.5% (208 / 220)	
Evaluable for lobar exclusion % (n / N)		98.5% (194 / 197)

Source: Attachment 3, Amended Statistical Analysis Report, Table 4:2

6.0 BASELINE SUBJECT CHARACTERISTICS

6.1 Demographic Data

The mean age of the 101 Control Subjects was 64.9 years and of the 220 Zephyr EBV Subjects the mean age was 65.3 years (p = 0.56). Weight and height were comparable; the mean BMI for Control Subjects was 24.8 kg/m^2 and for Zephyr EBV Subjects was 25.1 kg/m^2 (p = 0.51). Mean blood pressures for the two groups were nearly identical (p = 0.67 systolic and p = 0.49 for diastolic). Males predominated in the Zephyr EBV Subject group (60.4%) compared to the Control Subject group (48.5%), the difference was nearly significant (p = 0.052). Both groups were almost entirely Caucasian.

Table 11 Subject Demographics

Characteristic	Control	Zephyr EBV	
Continuous Measures	**Mean (SD) N Median (Min, Max)**	**Mean (SD) N Median (Min, Max)**	**p value [1]**
Age (years)	64.91 (5.84) 101 65.0 (48.0, 76.0)	65.34 (6.83) 220 66.0 (47.0, 77.0)	0.5623
Weight (kg) [2]	71.71 (13.41) 101 69.5 (44.0, 102.1)	73.11 (14.51) 219 73.3 (33.6, 106.1)	0.1602
Height (meters)	1.68 (0.10) 101 1.68 (1.52, 1.91)	1.70 (0.09) 220 1.71 (1.50, 1.88)	0.1245
BMI (kg/m^2) [3]	24.82 (3.39) 101 24.8 (17.2, 32.1)	25.09 (3.96) 220 25.4 (14.9, 33.0)	0.5056
Systolic BP (mm Hg) [4]	129.92 (16.36) 98 130.0 (96.0, 171.0)	129.07 (16.71) 218 129.0 (91.0, 188.0)	0.6742
Diastolic BP (mm Hg) [4]	74.64 (9.98) 98 75.0 (50.0, 99.0)	73.84 (9.40) 218 73.0 (40.0, 100.0)	0.4935
Categorical Measures	**% (n / N)**	**% (n / N)**	**p value [5]**
Gender (Male)	48.5% (49 / 101)	60.4% (133 / 220)	0.0524
Race			1.0000
Caucasian	98.0% (99 / 101)	96.8% (213 / 220)	
African American	2.0% (2 / 101)	2.3% (5 / 220)	
Hispanic	0.0% (0 / 101)	0.5% (1 / 220)	
Asian	0.0% (0 / 101)	0.5% (1 / 220)	
Other	0.0% (0 / 101)	0.0% (0 / 220)	

[1] Two-sided t-test with equal variance
[2] One test subject did not have a weight recorded.
[3] BMI was computed in the case report form so it was available for all 220 test subjects even though weight was not recorded for 1 test subject.
[4] Blood pressure was not available for 3 control and 2 test subjects.
[5] Two-sided Fisher's exact test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:1

6.2 Pulmonary Medications

All subjects (100%) in both the Control Subject and Zephyr EBV Subject groups were taking bronchodilators, steroids and mucolytics upon study entry.

Table 12 Baseline Pulmonary Medications

Characteristic	Control % (n/N)	Zephyr EBV % (n/N)
Bronchodilators	100.0% (101 / 101)	100.0% (220 / 220)
Steroids	100.0% (101 / 101)	100.0% (220 / 220)
Mucolytics	100.0% (101 / 101)	100.0% (220 / 220)

Source: Attachment 3, Amended Statistical Analysis Report, Table 6:2

6.3 Medical History

Key medical factors were similar between the Control Subjects and Zephyr EBV Subjects. Diabetes was present in 5.0% of Control Subjects and 7.7% of Zephyr EBV Subjects ($p = 0.48$). An abnormal ECG upon study enrollment was found in 42.6% of Control Subjects and 45.9% of Zephyr EBV Subjects ($p = 0.63$). All but three study subjects had a history of smoking (98.0% Control Subjects, 99.6% Zephyr EBV Subjects, $p = 0.23$), with similar years of smoking (36.1 and 37.7 years respectively, $p = 0.17$) and pack-years (61.7 and 63.3 pack-years respectively, $p = 0.64$).

Table 13 Baseline Medical History

Characteristic	Control	Zephyr EBV	p value [1]
Diabetes % (n/N)	5.0% (5 / 101)	7.7% (17 / 220)	0.4777
Abnormal ECG % (n/N)	42.6% (43 / 101)	45.9% (101 / 220)	0.6294
Smoking % (n/N)	98.0% (99 / 101)	99.6% (219 / 220)	0.2339
Years of smoking [2]			
Mean (SD) N	36.12 (8.62) 100	37.74 (8.95) 217	0.1714
Median (Min, Max)	36.5 (10.0, 50.0)	39.0 (15.0, 60.0)	
Packs-years [3]			
Mean (SD) N	61.67 (30.33) 98	63.29 (29.58) 216	0.6355
Median (Min, Max)	60.0 (10.0, 168.0)	60.0 (12.5, 184.0)	

[1] For continuous variables, the two-sided t-test with equal variance was used and for categorical variables, two-sided Fisher's exact test.
[2] Years smoked was not reported for 2 test subjects who stated they were smokers.
[3] Packs smoked was not reported for 2 control and 3 test subjects who stated they were smokers.
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:2

6.4 Use of Supplemental Oxygen

Supplemental oxygen use was also not different between the two study groups, with 41.7% of Control Subjects and 43.9% of Zephyr EBV Subjects using oxygen ($p = 0.77$).

Hours of oxygen use daily were similar at rest (7.1 and 7.7 hours respectively, p = 0.49), during exertion (2.7 and 2.2 hours respectively, p = 0.28) and while sleeping (6.8 and 6.7 hours respectively, p = 0.79). Oxygen flow rates were also equivalent at rest (1.5 and 1.4 liters / min, p = 0.58), during exertion (2.6 and 2.4 liters / min, p = 0.22) and while sleeping (2.0 and 1.9 liters / min, p = 0.21).

Table 14 Use of Supplemental Oxygen

Characteristic		Control	Zephyr EBV	p value [1]
		% (n / N)	% (n / N)	
Subjects on continuous O_2 [2]		41.7% (30 / 72)	43.9% (65 / 148)	0.7736
		Mean (SD) N Median (Min, Max)	Mean (SD) N Median (Min, Max)	
Hours / Day [3]	Rest	7.13 (6.45) 65 8.0 (0.0, 19.0)	7.66 (6.74) 131 8.0 (0.0, 19.0)	0.4921
	Exertion	2.72 (2.74) 65 2.0 (0.0, 12.0)	2.22 (2.28) 140 1.5 (0.0, 14.0)	0.2803
	Sleep	6.81 (2.64) 64 8.0 (0.0, 10.0)	6.66 (3.00) 138 8.0 (0.0, 12.0)	0.7924
Flow (l / min) [4]	Rest	1.48 (1.20) 69 2.0 (0.0, 3.5)	1.43 (1.24) 134 2.0 (0.0, 5.0)	0.5805
	Exertion	2.59 (1.25) 69 2.5 (0.0, 6.0)	2.43 (1.36) 148 2.0 (0.0, 8.0)	0.2228
	Sleep	1.96 (0.85) 69 2.0 (0.0, 3.5)	1.85 (0.96) 144 2.0 (0.0, 5.0)	0.2142

[1] For continuous variables, the two-sided t-test with equal variance was used and for categorical variables, two-sided Fisher's exact test.
[2] Continuous O_2 use was not reported for 29 control and 72 test subjects.
[3] Continuous O_2 rest hours/day was not reported for 6 control and 17 test subjects, exertion hours/day was not reported for 6 control and 8 test subjects, and sleep hours/day was not reported for 7 control and 10 test subjects who reported on continuous O_2 use.
[4] Continuous O_2 flow was not reported for 2 control and 14 test subjects, exertion flow was not reported for 2 control and 0 test subjects, and sleep flow was not reported for 2 control and 4 test subjects who reported on continuous O_2 use.
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:2

6.5 Lung Function Parameters

There were no significant differences in any baseline lung function parameters between the Control Subjects and the Zephyr EBV Subjects. FEV_1 and FEV_1 % Predicted were respectively 0.84 liters and 30% in Control Subjects and 0.87 liters and 30% in Zephyr EBV Subjects. FVC and FVC % Predicted were respectively 2.62 liters and 70% in Control Subjects and 2.71 liters and 70% in Zephyr EBV Subjects. DL_{CO} and DL_{CO} % Predicted were respectively 10.15 mL CO / min / mmHg and 36% in Control Subjects and 9.52 mL CO / min / mmHg and 33% in Zephyr EBV Subjects. RV and RV %

Predicted were respectively 4.63 liters and 212% in Control Subjects and 4.79 liters and 216% in Zephyr EBV Subjects.

Table 15 Baseline Lung Functions

	Control		Zephyr EBV		
Characteristic	**Mean (SD) N Median (Min, Max)**	**Number Missing[1]**	**Mean (SD) N Median (Min, Max)**	**Number Missing[1]**	**p value [2]**
FEV_1 (liters)	0.84 (0.25) 101 0.78 (0.42, 1.56)	0	0.87 (0.26) 220 0.81(0.38, 1.62)	0	0.3150
FEV_1 % Predicted	30% (8%) 101 29% (15, 50%)	0	30% (8%) 219 29% (16, 51%)	1	0.9979
FVC (liters)	2.62 (0.82) 101 2.40 (1.11, 5.02)	0	2.71 (0.78) 220 2.59 (1.17, 5.53)	0	0.2783
FVC % Predicted	70% (16%) 101 69% (34, 111%)	0	70% (15%) 219 68% (38, 124%)	1	0.9245
FEV_1 / FVC	0.33 (0.07) 101 0.33 (0.20, 0.51)	0	0.33 (0.06) 220 0.32 (0.20, 0.52)	0	0.6048
DL_{CO} (ml CO / min / mm Hg)	10.15 (5.69) 101 9.15 (4.46, 56.31)	0	9.52 (3.11) 220 9.00 (3.30,21.92)	0	0.6807
DL_{CO} % Predicted	36% (16%) 101 34% (18, 166%)	0	33% (9%) 220 32% (14, 64%)	0	0.1138
VTG (liters)	5.65 (1.32) 100 5.32 (3.24, 8.99)	1	5.84 (2.25) 217 5.75 (2.75, 9.73)	3	0.1274
RV (liters)	4.63 (1.20) 100 4.38 (2.63, 8.52)	1	4.79 (1.15) 217 4.63 (2.34, 9.41)	3	0.1590
RV % Predicted	212% (47%) 100 202% (120, 362%)	1	216% (44%) 217 210% (117, 377%)	3	0.2839
TLC (liters)	7.37 (1.55) 100 6.97 (4.96, 11.77)	1	7.60 (1.44) 217 7.65 (4.80, 11.85)	3	0.1177
TLC % Predicted	125% (16%) 100 125% (92, 171%)	1	124% (15%) 217 123% (95, 165%)	3	0.6208
RV / TLC	0.63 (0.08) 100 0.63 (0.43, 0.82)	1	0.63 (0.09) 217 0.63 (0.35, 0.88)	3	0.8160
IC (liters)	1.72 (0.60) 100 1.62 (0.67, 3.55)	1	1.75 (0.57) 217 1.66 (0.47, 3.64)	3	0.4753
VC (liters)	2.75 (0.87) 100 2.57 (1.28, 5.23)	1	2.79 (0.86) 217 2.70 (0.96, 6.32)	3	0.4950

[1] The number missing is the number of subjects not reporting a value for the variable being measured.
[2] Two-sided t-test with equal variance
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:3

6.6 Arterial Blood Gas Analysis

Baseline arterial blood gas values were largely similar between the Control Subjects and the Zephyr EBV Subjects. The partial pressure of oxygen (68.4 and 69.1 mmHg, p = 0.51) and the oxygen saturation (93% and 93%, p = 0.71) were not different, nor was the

pH (7.42 and 7.43, p = 0.48). However, the Control Subjects had a slightly higher mean partial pressure of carbon dioxide (41.6 compared with 40.5 mmHg, p = 0.044) and a borderline higher bicarbonate (26.9 compared with 26.3 mEq / liter, p = 0.09).

Table 16 Baseline Arterial Blood Gas Analysis

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
PaO_2 (mm Hg)	68.44 (8.09) 100 69.0 (54.0, 90.0)	69.14 (10.26) 220 68.0 (47.7, 111.0)	0.5138
$PaCO_2$ (mm Hg)	41.61 (4.82) 100 42.0 (26.8, 51.0)	40.53 (4.25) 220 40.25 (30.0, 51.0)	0.0440
pH	7.42 (0.03) 101 7.42 (7.36, 7.50)	7.43 (0.03) 220 7.42 (7.35, 7.51)	0.4752
Bicarbonate (mEq / liter)	26.85 (2.71) 101 26.5 (19.6, 34.1)	26.30 (2.66) 217 26.0 (19.1, 35.5)	0.0894
Oxygen saturation (%)	93% (3%) 97 94% (78, 98%)	93% (3%) 215 94% (85%, 100%)	0.7130

[1] t-test with equal variance Source: Attachment 3, Amended Statistical Analysis Report, Table 6:4

6.7 BODE Indices

Baseline BODE Index scores were quite similar between Control Subjects and Zephyr EBV Subjects, 4.2 and 4.4 respectively (p = 0.2551).

Table 17 Baseline BODE Indices

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
BODE Index	4.2 (1.3) 92 4.0 (2.0, 8.0)	4.4 (1.6) 198 4.0 (1.0, 9.0)	0.2551

[1] Two-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.13

6.8 SGRQ Scores

Baseline SGRQ scores were quite similar between Control Subjects and Zephyr EBV Subjects, 50.1 and 51.5 respectively (p = 0.3236).

Table 18 Baseline SGRQ Scores

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
SGRQ Scores	50.1 (12.3) 89 50.6 (23.3, 80.7)	51.5 (13.9) 203 51.6 (5.8, 78.6)	0.3236

[1] Two-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.14

6.9 mMRC Dyspnea Scale Scores

Baseline mMRC dyspnea scores were identical for Control Subjects and Zephyr EBV Subjects, 1.7 and 1.7 respectively ($p = 0.7748$).

Table 19 Baseline mMRC Dyspnea Scale Scores

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
mMRC Scores	1.7 (0.8) 92 2.0 (0.0, 4.0)	1.7 (0.9) 199 2.0 (0.0, 4.0)	0.7748

[1] Two-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.15

6.10 Exercise Tolerance

Baseline exercise tolerance was the same between the two study groups. The Control Subjects had a slightly lower peak workload on cycle ergometry (43.2 versus 45.0 watts, $p = 0.71$). However, the Control Subjects showed a slightly longer 6MWT (350.9 versus 333.9 meters, $p = 0.15$).

Table 20 Baseline Exercise Tolerance

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
Peak Workload on Cycle Ergometry (watts)	43.2 (21.3) 101 40.0 (5.0, 120.0)	45.0 (23.9) 220 40.0 (5.0, 135.0)	0.7149
6MWT Distance (m)	350.9 (83.2) 101 344.0 (192.0, 598.6)	333.9 (87.4) 220 335.1 (140.0, 563.9)	0.1479

[1] Two-sided t-test with equal variance
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:5

6.11 Borg Test Results

Dyspnea and fatigue were rated on a scale from 0 to 10 during exercise testing (Borg Test) at baseline, and there were no significant differences in dyspnea or fatigue scores before or after performing the 6MWT, as noted in the Table below.

Table 21 Baseline Borg Testing Results

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
Dyspnea before 6MWT	1.0 (1.1) 96 0.5 (0.0, 5.0)	1.0 (1.3) 207 0.5 (0.0, 8.0)	0.6291
Dyspnea after 6MWT	4.0 (2.1) 97 3.0 (1.0, 10.0)	4.2 (2.1) 209 4.0 (0.0, 10.0)	0.2675
Fatigue before 6MWT	1.1 (1.5) 96 0.5 (0.0, 8.0)	1.1 (1.5) 203 0.5 (0.0, 8.0)	0.6130
Fatigue after 6MWT	3.0 (2.1) 96 3.0 (0.0, 8.0)	3.1 (2.2) 205 3.0 (0.0, 10.0)	0.8264

[1] The two-sided Wilcoxon rank sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6:6

6.12 HRCT Characteristics

The degree of emphysematous destruction was rated by the Core Radiology on a scale from 0% to 100% — 0% indicating no emphysematous destruction in that lobe, 100% indicating complete destruction. There were no differences in Density Score by lobe between the two study groups (see Table 22).

Table 22 Baseline Disease Distribution (Density Score by Lobe)

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value
Right Upper Lobe DS (%)	63.2 (14.9) 101 64.0 (23.0, 90.0)	64.8 (14.2) 220 67.0 (9.0, 89.0)	0.3563 [1]
Right Middle Lobe DS (%)	54.6 (17.3) 101 57.0 (16.0, 85.0)	53.1 (17.9) 220 56.0 (0.0, 86.0)	0.5164 [1]
Right Lower Lobe DS (%)	49.2 (17.2) 101 50.0 (10.0, 83.0)	47.1 (17.6) 220 45.0 (3.0, 91.0)	0.3220 [2]
Left Upper Lobe DS (%)	60.0 (13.4) 101 61.0 (18.0, 85.0)	60.1 (13.2) 220 62.0 (16.0, 87.0)	0.8430 [1]
Left Lower Lobe DS (%)	47.5 (17.2) 101 49.0 (4.0, 80.0)	45.7 (18.7) 220 47.0 (5.0, 85.0)	0.4181 [1]

[1] Two-sided Wilcoxon rank-sum test
[2] Two-sided t-test with equal variance

Source: Attachment 3, Amended Statistical Analysis Report, Table 6.16

Similarly, the volume of each lobe was evaluated by the Core Radiology Lab. The distribution of volume by lobe was quite similar between the two study groups (see Table 23).

Table 23 Baseline Volume by Lobe (liters) at TLC

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value
Right Upper Lobe Volume	1.56 (0.43) 101 1.48 (0.79, 2.94)	1.63 (0.48) 220 1.54 (0.53, 3.65)	0.2366 [1]
Right Middle Lobe Volume	0.45 (0.18) 101 0.43 (0.01, 1.03)	0.49 (0.21) 220 0.46 (0.00, 1.23)	0.1199 [2]
Right Lower Lobe Volume	1.53 (0.43) 101 1.45 (0.56, 3.12)	1.56 (0.45) 220 1.51 (0.71, 3.83)	0.6544 [1]
Left Upper Lobe Volume	1.69 (0.45) 101 1.62 (0.94, 3.11)	1.78 (0.48) 220 1.72 (0.81, 3.17)	0.0883 [1]
Left Lower Lobe Volume	1.50 (0.45) 101 1.46 (0.62, 2.74)	1.52 (0.42) 220 1.49 (0.76, 2.86)	0.5829 [1]

[1] Two-sided Wilcoxon rank-sum test
[2] Two-sided t-test with unequal variance
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.17

There were no differences in Target Lobe Density Score (DS) ($p = 0.2087$), Heterogeneity Score ($p = 0.3534$), Target Lobe Volume ($p = 0.3055$), and Ipsilateral Lung, Non-target Lobe Volume (0.3334).

Table 24 Target-specific Baseline HRCT Characteristics

Characteristic	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	p value [1]
Target Lobe Density Score (%)	66.9 (10.9) 101 66.0 (51.0, 89.0)	68.5 (10.2) 220 68.0 (51.0, 91.0)	0.2087
Heterogeneity Score (%)	15.0 (16.7) 101 15.0 (-20.0, 58.0)	17.1 (15.2) 220 15.0 (-19.0, 74.0)	0.3534
Target Lobe Volume (L)	1.73 (0.45) 101 1.67 (0.79, 2.94)	1.81 (0.51) 220 1.76 (0.81, 3.83)	0.3055
Ipsilateral Lung, Non-target Lobe Volume (L)	1.69 (0.50) 101 1.60 (0.66, 2.91)	1.73 (0.46) 220 1.70 (0.72, 3.25)	0.3334

[1] Two-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.18

The proportion of subjects in the Control Group with Complete Fissures was nominally higher than the Zephyr EBV Group, but this difference did not reach significance (p = 0.2542).

Table 25 Proportion of Complete Fissures (vs. Partial or Absent)

Characteristic	Control % (n / N)	Zephyr EBV % (n / N)	p value [1]
Complete Fissure Score [2]	45.2 (42 / 93)	38.0 (79 / 208)	0.2542

[1] Two-sided Fisher's exact test
[2] For Complete Fissure on right lung, both Right Horizontal and Right Oblique Fissures must be Complete.
Source: Attachment 3, Amended Statistical Analysis Report, Table 6.19

6.13 Summary: Study Population

The VENT Pivotal Trial population achieved its intended target population of subjects with severe emphysema:

- FEV_1 % predicted = 30% both groups
- FEV_1 / FVC = 0.33 both groups
- RV % predicted 212% (Control) and 216% (Zephyr EBV)

Randomization was successful overall: 31.5% Control Subjects and 68.5% Zephyr EBV Subjects, close to the intended rate of 1:2. Randomization was well balanced across study sites and strata of exercise capacity and target lobe location.

Review of demographic data, use of pulmonary medications, medical history, use of supplemental oxygen, lung functions, arterial blood gas results, exercise tolerance, Borg test results, BODE indices, SGRQ scores, mMRC Dyspnea Scale scores, and HRCT characteristics were all comparable between Control Subjects and Zephyr EBV Subjects.

These results confirm that the screening and randomization procedures utilized by the VENT Pivotal Trial resulted in the enrollment of adult subjects with severe emphysema into two highly comparable study groups. Those few parameters showing significant or near significant differences were included in multivariate analyses of study outcomes as discussed in subsequent sections.

7.0 ZEPHYR EBV IMPLANTATION PROCEDURE

7.1 Introduction

The Zephyr EBV Implantation Procedure was characterized for the Zephyr EBV Subjects by a number of acute assessments. These included:

- 7.2. Procedure Details
  - 7.2.1. Procedure Time
  - 7.2.2. Target Lobes
  - 7.2.3. Anesthesia and Airway Management
  - 7.2.4. Proportion of Procedures Involving a Rigid Bronchoscope
- 7.3. Procedure Outcomes
  - 7.3.1. Number of Zephyr EBVs Placed Per Subject
  - 7.3.2. Acute Technical Success (Site Determined)
  - 7.3.3. Valves Removed and Replaced During the Initial Procedure
  - 7.3.4. Device Malfunctions
- 7.4. Summary: Zephyr EBV Implantation Procedure

A detailed presentation for each of these procedural parameters and outcomes follows in this section of the Clinical Study Report.

7.2 Procedure Details

7.2.1 Procedure Time

The mean procedure duration—the time between bronchoscope insertion and bronchoscope removal—was 33.8 minutes (median 28 minutes, range 6 to 100 minutes).

Table 26 Zephyr Endobronchial Valve Procedure Time

Zephyr EBV Subjects	Mean (SD) N [1] Median (Min, Max)
Procedure time (min)	33.8 (20.5) 212 28.0 (6, 100)

[1] Denominator is the 212 Zephyr EBV Subjects with procedure time data.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.2.2 Target Lobes

Target lobes were defined by pre-procedural imaging assessments. Target lobes were largely in the upper lobes (76.6%) and predominantly in the right side (61.6%). The right

upper lobe was the target in 52.3% of Zephyr EBV Subjects, the right lower lobe in 9.3%, the left upper lobe in 24.3%, and the left lower lobe in 14.0%.

Table 27 Zephyr Endobronchial Valve Target Lobes

Zephyr EBV Subjects	% (n / N) [1]
Target Lobe	
Right upper lobe (RUL)	52.3% (112 / 214)
Right lower lobe (RLL)	9.3% (20 / 214)
Left upper lobe (LUL)	24.3% (52 / 214)
Left lower lobe (LLL)	14.0% (30 / 214)

[1] Denominator is the 214 Zephyr EBV Subjects who underwent procedure; 6 subjects randomized to the Zephyr EBV Subjects Group did not undergo a Zephyr EBV implantation procedure.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.2.3 Anesthesia and Airway Management

Conscious sedation was used during the implantation procedure in 71.5% of subjects, with the remaining 28.5% having general anesthesia. This choice of anesthesia was reflected in the proportion of subjects who were intubated (35.1%) or ventilated (29.9%) during the implantation procedure.

Table 28 Anesthesia and Airway Management

Zephyr EBV Subjects	% (n / N) [1]
Anesthesia	
General	28.5% (61 / 214)
Conscious sedation	71.5% (153 / 214)
Intubated during procedure	
Yes	35.1% (75 / 214)
No	64.9% (139 / 214)
Ventilated during procedure	
Yes	29.9% (64 / 214)
No	70.1% (150 / 214)

[1] Denominator is the 214 Zephyr EBV Subjects who underwent procedure; 6 subjects randomized to the Zephyr EBV Subjects Group did not undergo a Zephyr EBV implantation procedure.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.2.4 Proportion of Procedures Involving a Rigid Bronchoscope

Three (3) Zephyr EBV Subjects had a rigid bronchoscope used during the Zephyr EBV implantation procedure, the remaining 211 procedures involved only flexible bronchoscopy.

Table 29 Proportion of Procedures Involving a Rigid Bronchoscope

Zephyr EBV Subjects	% (n / N) [1]
Rigid bronchoscope used	
Yes	1.4% (3 / 214)
No	98.6% (211 / 214)

[1] Denominator is the214 Zephyr EBV Subjects who underwent procedure; 6 subjects randomized to the Zephyr EBV Subjects Group did not undergo a Zephyr EBV implantation procedure.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.3 Procedure Outcomes

7.3.1 Number of Zephyr EBVs Placed Per Subject

A total of 820 valves was placed in Zephyr EBV Subjects. The mean number of valves placed per Zephyr EBV subject was 3.8 (median 4.0, range 1 to 9).

Table 30 Number of Zephyr EBVs Placed Per Subject

Zephyr EBV Subjects	Mean (SD) N [1 2] Median (Min, Max)
Number of valves placed	3.83 (1.39) 214 4.0 (1.0, 9.0)

[1] Denominator is the 214 Zephyr EBV Subjects who underwent procedure; 6 subjects randomized to the Zephyr EBV Subjects Group did not undergo a Zephyr EBV implantation procedure.
[2] Average valves implanted are net of valves removed intra-procedure
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

7.3.2 Acute Technical Success (Site Determined)

Acute Technical Success—determined by the implanting site at the time of the procedure, based on the Investigator's bronchoscopic assessment of complete exclusion of the target lobe—was found in 94.9% of subjects.

Table 31 Acute Technical Success (Site Determined)

Zephyr EBV Subjects	% (n / N) [1]
Acute Technical Success	94.9% (203 / 214)

[1] Denominator is the 214 Zephyr EBV Subjects who underwent procedure; 6 subjects randomized to the Zephyr EBV Subjects Group did not undergo a Zephyr EBV implantation procedure.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

Eleven (11) Zephyr EBV Subjects had acute technical failure, based on an inability to obtain complete lobar exclusion of the target lobe. The reasons for technical failure were: segment too small for valve (27.3%), unable to place valve (36.4%), side branch airway too small (9.1%), unable to valve apical segment, (18.2%), and other (9.1%). The Acute Technical Failures are listed in the table below.

Table 32 Reasons for Acute Technical Failure (Site Determined)

EBV Group	% (n / N) [1]
Procedural Failures	100.0% (11 / 11)
Segment too small for valve	27.3 % (3 / 11)
Unable to place valve	36.4% (4 / 11)
Other	9.1% (1 / 11)
Side branch airway too small	9.1% (1 / 11)
Unable to valve apical segment	18.2% (2 / 11)

[1] Denominator is the site reported failures to achieve complete lobar exclusion.
Source: Attachment 3, Amended Statistical Analysis Report, Table 7:1

Table 33 Listing of Acute Technical Failures

Subject ID	Reason for Failure to Achieve Lobar Exclusion
	Small side branch airway could not be occluded
	B6a segment was too small to place a valve
	Valve could not be placed in one of the subsegments of the superior bronchus due to the severe angle of the airway
	B7 segment was too small for valve placement.
	Unable to cannulate B1 and this segment was not treated.
	Unable to place a valve in segment LB6c, but segment was partially occluded by other valves
	Unable to place a valve in RB1b due to severe angle of segment
	Following valve deployment in RB1b2, a hole was revealed in the airway
	Initially placed valves in B1a and B1b nested together and had to be removed; Investigator unable to valve the more proximal B1 segment
	B6c segment was too small for valve
	One lumen was too large

Source: P070025, September 21, 2007, Volume 011, Page 85

7.3.3 Valves Removed and Replaced During the Initial Procedure

Ninety-six (96) Zephyr EBV subjects had a total of 143 valves removed during the procedure.

In 89 of these 96 subjects (92.7%), the valves removed during the procedure were successfully replaced during that same procedure with one or more new valves, which led to Acute Technical Success as reported by the site. Seven (7) of the 96 subjects (7.3%) did not go on to Acute Technical Success for the following reasons: lumen too large (1 / 7), lumen too small (2 / 7), small side branch could not be occluded (2 / 7), and unable to place valve in segment due to severe angle of airway (2 / 7).

Table 34 Subjects with Valves Removed During the Initial Procedure and Not Replaced (Technical Failures)

	% (n / N) [1]
Zephyr EBV Subjects	100.0% (7 / 7)
Lumen too large	14.3% (1 / 7)
Lumen too small	28.6% (2 / 7)
Small side branch could not be occluded	28.6% (2 / 7)
Severe angulation	28.6% (2 / 7)

[1] Denominator is 7 Zephyr EBV Subjects from Table 27 above with valves removed during the initi

Source: P070025, September 21, 2007, Volume 011, Page 86

Of the 143 valves removed during the initial procedure, 92.3% were for valve positioning: 48.9% were placed too proximally, 19.6% too distally and 3.5% were too small for the selected airway. Other removals for sizing or positioning reasons accounted for 20.3% of valves removed during the initial procedure and included: valve was dislodged while removing other valves, valves placed in wrong airway, first valve placed interfering with placement of other valves, valve was too large for the selected airway, and incomplete exclusion. Valve or deployment reasons for removal accounted for 7.7% of valves removed during the initial procedure and included: valve appeared non-functional, valve did not deploy properly, valve loaded and deployed backwards, and duckbill appeared inverted.

Table 35 Valves Removed During the Initial Procedure

Zephyr EBV Treatment	% (n / N) [1]
Total Valves Removed	100.0% (143 / 143)
Size / Positioning	92.3% (132 / 143)
Placed too proximally	48.9% (70 / 143)
Placed too distally	19.6% (28 / 143)
Valve too small	3.5% (5 / 143)
Other – Size / Positioning	20.3% (29 / 143)
Valve / Deployment	7.7% (11 / 143)

[1] Denominator is 143 valves removed during the initial Zephyr EBV implantation procedure.
Source: P070025, September 21, 2007, Volume 011, Page 86

7.3.4 Device Malfunctions

There were device malfunctions in 21 (9.8%) of Zephyr EBV procedures, and 1 device malfunction in a follow-up procedure to replace an expectorated valve. For the total of 22 subjects with any device malfunction, 35 devices were reported as malfunctioning (18 EBVs, 15 EDCs and 2 ELSs). The majority of the malfunctions were associated with Loading Failures and Delivery Failure due to Anatomical Constraints; the primary reasons for these device malfunctions are summarized in the following Table.

Table 36 Categories of Device Malfunctions

Zephyr EBV Group	% (n / N) [1]
Procedures with Device Malfunctions	100.0% (22 / 22)
Loading Failure	45.5% (10 / 22)
Delivery Failure / Anatomical	31.8% (7 / 22)
Deployment Failure	9.1% (2 / 22)
Iatrogenic Injury	4.5% (1 / 22)
Other / Unknown	9.1% (2 / 22)

[1] Denominator is with device malfunctions: 21 during the initial Zephyr EBV implantation procedure and 1 during follow-up bronchoscopy to replace an expectorated valve.
Source: P07002 21, 2007, Volume 011, Page 87

The following Table lists those subjects whose procedure was associated with a device malfunction. Of the 22 malfunctions reported, 21 did not have adverse events associated with the malfunction. In one procedure an airway perforation was reported.

Table 37 Listing of Device Malfunctions

Subject ID	EBV	EDC	ELS	Failure Category	Sequelae
	1			Delivery Failure / Anatomical	None
	1			Other	None
	1			Delivery Failure / Anatomical	None
		2		Loading Failure	None
	2	1		Loading Failure	None
	2	1		Loading Failure	None
	1			Delivery Failure / Anatomical	None
	1			Delivery Failure / Anatomical	None
	1			Deployment Failure	None
		1		Deployment Failure	None
	1	1	1	Loading Failure	None
	1			Other	None
	1			Delivery Failure / Anatomical	None
	2	2		Loading Failure	None
	1	1	1	Loading Failure	None
		1		Loading Failure	None
		1		Delivery Failure / Anatomical	None
		1		Delivery Failure / Anatomical	None
		1		Iatrogenic Injury (Airway Perforation)	SAE
	1	1		Loading Failure	None
		1		Loading Failure	None
	1			Loading Failure	None
Totals	**18**	**15**	**2**		

Source: P070025, September 21, 2007, Volume 011, Page 88

7.4 Summary: Zephyr EBV Implantation Procedure

The mean procedure duration—the time between bronchoscope insertion and bronchoscope removal—was 33.8 minutes (median 28 minutes, range 6 to 100).

Target lobes were defined by pre-procedural imaging assessments. Target lobes were largely in the upper lobes (76.6%) and predominantly in the right side (61.6%). The right upper lobe was the target in 52.3% of Zephyr EBV Subjects, the right lower lobe in 9.3%, the left upper lobe in 24.3%, and the left lower lobe in 14.0%.

Conscious sedation was used during the implantation procedure in 71.5% of subjects, with the remaining 28.5% having general anesthesia. This choice of anesthesia was

reflected in the proportion of subjects who were intubated (35.1%) or ventilated (29.9%) during the implantation procedure.

Three (3) Zephyr EBV Subjects had a rigid bronchoscope used during the Zephyr EBV implantation procedure, the remaining 211 procedures involved only flexible bronchoscopy.

The mean number of valves placed per Zephyr EBV Subject was 3.8 (median 4, range 1 to 9).

Acute Technical Success—determined by the implanting site at the time of the procedure, based on the Investigator's assessment of complete exclusion of the target lobe—was found in 94.9% of subjects.

Of the 214 Zephyr EBV Subjects who received one or more valves during the initial study procedure, 96 subjects had a total of 143 valves removed during the procedure. In 89 of these 96 subjects (92.7%), the valves removed during the procedure were successfully replaced with one or more valves, which led to Acute Technical Success (lobar exclusion) as reported by the site.

Of the 143 valves removed during the initial procedure, 92.3% were for valve positioning: 48.9% were placed too proximally, 19.6% too distally and 3.5% were too small for the selected airway. Other removals for sizing or positioning reasons accounted for 20.3% of valves removed during the initial procedure and included: valve was dislodged while removing other valves, valves placed in wrong airway, first valve placed interfering with placement of other valves, valve was too large for the selected airway, and incomplete exclusion. Valve or deployment reasons for removal accounted for 7.7% of valves removed during the initial procedure and included: valve appeared non-functional, valve did not deploy properly, valve loaded and deployed backwards, and duckbill appeared inverted.

There were device malfunctions in 21 (9.8%) of Zephyr EBV procedures, and 1 device malfunction in a follow-up procedure to replace an expectorated valve. For the total of 22 subjects with any device malfunction, 35 devices were reported as malfunctioning (18 EBVs, 15 EDCs and 2 ELSs). The majority of the malfunctions were associated with Loading Failures and Delivery Failure due to Anatomical Constraints.

Overall the Zephyr EBV system was easy to use, reliable and successful in achieving lobar exclusion at the time of the initial procedure.

8.0 PRIMARY AND SECONDARY EFFECTIVENESS OUTCOMES

8.1 Introduction

The VENT Pivotal Study protocol and Statistical Analysis Plan specified a Primary Effectiveness Outcome and four Secondary Effectiveness Outcomes. The effectiveness of the Zephyr Endobronchial Valve in the treatment of subjects with severe heterogeneous emphysema was assessed by a number of analyses, as detailed in the following Section 8 outline:

- 8.2. Primary Effectiveness Outcomes
  - 8.2.1. Percent Change in FEV_1 and 6MWT – Multiple-Imputation Intent-to-Treat
  - 8.2.2. Completed Cases: Percent Change in FEV_1 and 6MWT
- 8.3. Secondary Effectiveness Outcomes
  - 8.3.1. Change in St. George's Respiratory Questionnaire Score
  - 8.3.2. Change in mMRC Dyspnea Scale
  - 8.3.3. Change in Maximum Workload during Cycle Ergometry
  - 8.3.4. Change in Use of Supplemental Oxygen
- 8.4. Summary: Primary and Secondary Effectiveness Outcomes

8.2 Primary Effectiveness Outcomes

A primary objective of the VENT Pivotal Trial was to assess the effectiveness of the Zephyr EBV in treating subjects with severe heterogeneous emphysema.

This was to be measured by determining the FEV_1 and 6MWT values at baseline and at 6 months, and to compare the percentage change from baseline in these tests between the Control Subjects and the Zephyr EBV Subjects. Inference testing using multiple-imputation, intent-to-treat (ITT) analysis with a one-sided superiority test at a significance level of 0.025 for each of the two co-primary effectiveness measures was employed.

8.2.1 Percent Change in FEV_1 and 6MWT – Multiple Imputation

The VENT Pivotal Trial met its Primary Effectiveness Outcome in favor of Zephyr EBV treatment by multiple-imputation, intent-to-treat analysis. For this analysis, both FEV_1 and 6MWT percent changes from baseline to 6 months were significantly greater in the Zephyr EBV Subjects compared to the Control Subjects. The mean percent change in

FEV_1 was 6.8% greater for Zephyr EBV Subjects compared with Control Subjects (p = 0.002) and the median percent change in 6MWT was 5.8% greater for Zephyr EBV Subjects compared with Control Subjects (p = 0.019).

Table 38 Primary Effectiveness Outcome: Multiple-Imputation, Intent-to-Treat Percent Change in FEV_1 and 6MWT at 6 Months

Primary Effectiveness Outcome	Delta (%) (95% CI)	p value
Percent Change in FEV_1	6.8 [1] (2.1, 11.5)	**0.002 [2]**
Percent Change in 6MWT	5.8 [3] (0.5, 11.2)	**0.019 [4]**

[1] Multiple-imputation difference in means and confidence interval.
[2] Multiple-imputation combined parametric p-value.
[3] Multiple-imputation point estimate of difference in medians and confidence interval.
[4] Multiple-imputation combined non-parametric p-value.
Source: Attachment 3, Amended Statistical Analysis Report, Table 9:1.

8.2.2 Completed Cases: Percent Change in FEV_1 and 6MWT

The intent-to-treat imputations were confirmed by a Completed Cases analysis. Completed Cases subjects were defined as the subset of all randomized and eligible subjects who received study-directed treatment and who had 6 months of follow-up. No imputation was required for this analysis.

Zephyr EBV Subjects had a significantly greater percent improvement in both FEV_1 and 6MWT from baseline to 6 months compared with Control Subjects.

<u>Completed Cases at 6 months:</u>
FEV_1: Control: −1.9%; Zephyr EBV: +5.3% (Δ = +7.2%, p = 0.0003)
6MWT: Control: −1.5%; Zephyr EBV: +4.3% (Δ = +5.8%, p = 0.0079)

Table 39 Completed Cases: Percent Change in FEV_1 and 6MWT at 6 Months

Percent Change from Baseline		Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
Completed Cases	**FEV_1**	−1.9 (12.2) 75 −3.4 (−27.7, 38.6)	5.3 (19.6) 179 3.8 (−38.3, 78.9)	7.2 [1] (3.2, 11.2)	**0.0003 [2]**
	6MWT	−1.5 (22.5) 73 −2.3 (−54.9, 71.4)	4.3 (22.7) 178 3.5 (−83.3, 108.0)	5.8 [3] (1.3, 11.7)[4]	**0.0079 [5]**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference of medians
[4] Non-parametric confidence interval
[5] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Tables 10:1 and 10:2

8.3 Secondary Effectiveness Outcomes

The VENT Pivotal Trial specified four secondary effectiveness outcomes:

- Change in St. George's Respiratory Questionnaire score from baseline
- Change in Modified Medical Research Council Dyspnea Scale score from baseline
- Change in maximum workload during cycle ergometry from baseline
- Change in the use of supplemental oxygen from baseline

These outcomes, and related analyses, are summarized below.

8.3.1 Change in St. George's Respiratory Questionnaire Score

The St. George's Respiratory Questionnaire (SGRQ) is a standardized questionnaire for quality of life (QoL) assessment in airways disease, designed to allow comparative measurements of health between groups and to quantify changes in health following interventions. Three scales (Symptoms, Activity and Impacts) are combined into an overall score from 0 (best) to 100 (worst).

When the change from baseline in the SGRQ score was considered using multiple-imputation, Intent-to-Treat analysis, the Zephyr EBV Subjects had a mean 3.4 point improvement (score reduction) relative to Control Subjects (p = 0.0167). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 40 2° Effectiveness Outcome: Change in SGRQ Score at 6 Months

2° Outcome: SGRQ Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)[1]	p value[2]
Multiple-Imputation, Intent-to-Treat			–3.4 (-6.6, -0.3)	0.0167
CC Subjects	0.7 (9.7) 62 1.5 (–25.8, 27.9)	–2.7 (13.3) 158 –2.2 (–35.9, 55.0)	–3.4 (–6.6, –0.2)	0.0192

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:1.& 11.1a

8.3.2 Change in Modified Medical Research Council Dyspnea Scale

The Modified Medical Research Council Dyspnea Scale (mMRC) is a brief questionnaire designed to quantify the extent of dyspnea while performing activities of daily life, ranging from 0 (not troubled with breathlessness except during strenuous exercise) to 4 (too breathless to leave house, OR breathless when dressing/undressing).

When the change from baseline in the mMRC Dyspnea Scale was considered using the multiple imputation, Intent-to-Treat dataset, the Zephyr EBV Subjects had a mean 0.26 point improvement (score reduction) relative to Control Subjects (p = 0.0183). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 41 2° Effectiveness Outcome: Change in mMRC Dyspnea Scale at 6 Months

2° Outcome: mMRC Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Multiple-Imputation, Intent-to-Treat			–0.26 (–0.49, –0.02)	**0.0183**
CC Subjects	0.21 (0.83) 67 0.00 (–2.00, 2.00)	–0.09 (1.04)162 0.00 (–3.00, 3.00)	–0.30 (–0.56, –0.05)	**0.0108**

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1 & 11.1a

8.3.3 Change in Maximum Workload during Cycle Ergometry

Maximum exercise capacity in watts was determined by cycle ergometry in a testing protocol closely modeled on that used in the NETT study.

When the change from baseline in the maximum workload during cycle ergometry was considered using the multiple imputation, Intent-to-Treat dataset, the Zephyr EBV Subjects had a median 3.8 watt improvement relative to Control Subjects (p = 0.0203). These findings of significance were confirmed by Completed-Cases univariate and multivariate mixed-model analyses.

Table 42 2° Effectiveness Outcome: Change in Maximum Workload during Cycle Ergometry (watts) at 6 Months

2° Outcome: Cycle Ergometry – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
Multiple-Imputation, Intent-to-Treat			3.8 [1] (0.2, 7.4)	**0.0203** [2]
CC Subjects	–4.4 (12.8) 69 –5.0 (–40.0, 45.0)	0.1 (15.3) 166 0.0 (–110.0, 50.0)	5.0 [3] (0.0, 5.0)	**0.0044** [4]

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference of medians and non-parametric confidence interval
[4] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:1.&11.1a

8.3.4 Change in Use of Supplemental Oxygen

The change from baseline to 6 months in subject-reported supplemental oxygen use during various conditions (continuous, during rest, during sleep and during exertion) was compared between the Zephyr EBV Subjects and Control Subjects.

When the change from baseline in use of supplemental oxygen was considered using the multiple imputation, Intent-to-Treat dataset, the Zephyr EBV Subjects had a median 12.0 liter/day reduction in oxygen requirement relative to Control Subjects ($p = 0.0198$).

Mixed model, multivariate analysis of the Completed Cases dataset did not result in a significant main effect or interaction for Use of Supplemental Oxygen.

Table 43 2° Effectiveness Outcome: Use of Supplemental Oxygen (liters / day)

2° Outcome: Supplemental O_2 – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
Multiple-Imputation, Intent-to-Treat Subjects			–12.0 [1] (–76.7, 52.7)	**0.0198** [2]
CC Subjects	82.9 (744.0) 75 0.0 (-2220.0, 3360.0)	-17.1 (912.8) 171 0.0 (-3840.0, 3750.0)	-100.1 [3] (-318.6, 118.4)	0.1837 [4]

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
[3] Difference of means and unequal variance t-test confidence interval
[4] One-sided unequal variance t-test
Source: Attachment 3, Amended Statistical Analysis Report Table 25.1&.11.1a

8.4 Summary: 1° and 2° Effectiveness Outcomes

The VENT Pivotal Trial met its Primary Effectiveness Outcomes in favor of Zephyr EBV treatment by univariate testing, with a significantly better improvement in both FEV_1 and 6MWT in Zephyr EBV Subjects when compared to Control Subjects at 6 months of follow-up. These significant differences existed whether the analysis was performed with multiple imputation for missing values or with Completed Cases only.

ITT at 6 months:
FEV_1: $\Delta = +6.8\%$, $p = 0.002$
6MWT: $\Delta = +5.8\%$, $p = 0.019$

Completed Cases at 6 months:
FEV_1: $\Delta = +7.2\%$, $p < 0.001$
6MWT: $\Delta = +5.8\%$, $p = 0.008$

The Vent Pivotal Trial met its 4 secondary effectiveness outcomes: SGRQ, mMRC, cycle ergometry, and supplemental oxygen use.

- **The St. George's Respiratory Questionnaire (SGRQ)** showed significantly greater mean improvement (score reduction) for Zephyr EBV Subjects compared to the Control Subjects ($\Delta = -3.4$, $p = 0.0167$) at 6 months.
- **The Modified Medical Research Council Dyspnea Scale (mMRC)** showed significantly greater mean improvement (score reduction) for Zephyr EBV Subjects compared to the Control Subjects ($\Delta = -0.26$, $p = 0.0183$) at 6 months.
- **Maximum workload during cycle ergometry** showed significantly greater mean improvement for Zephyr EBV Subjects compared to the Control Subjects ($\Delta = 3.8$ watts, $p = 0.0203$).
- **Use of supplemental oxygen** showed a statistically-significant improvement in the self-reported use of supplemental oxygen in the Zephyr EBV Subjects compared to Control Subjects ($\Delta = -12.0$ L / day, $p = 0.0198$).

The VENT Pivotal Trial of unilateral treatment of severe heterogeneous emphysema in medically optimized subjects met its Primary Effectiveness Outcome and its 4 Secondary Effectiveness Outcomes, showing significantly better treatment group outcome measures in Zephyr EBV Subjects when compared to Control Subjects.

9.0 PRIMARY SAFETY OUTCOME

9.1 Introduction

The Primary Safety Outcome for the Zephyr EBV Pivotal Trial was the Major Complications Composite. This outcome measure was also subjected to several related analyses to clarify MCC experience over time and in relation to covariates.

- 9.2. Primary Safety Outcome: Major Complications Composite
- 9.3. Major Complications Composite: Related Analyses
  - 9.3.1. All-Cause Mortality
  - 9.3.2. Cox Regression Analysis of MCCs through Six Months
  - 9.3.3. MCCs by Time Period through One Year
  - 9.3.4. MCCs by Valve Removal Status through One Year
- 9.4. Summary: Primary Safety Outcome

9.2 Primary Safety Outcome: Major Complications Composite

The Primary Safety Outcome for the VENT Pivotal Trial was the proportion of subjects in each group with one or more Major Complications through 6 months of follow-up, using the mITT population. No *a priori* inference test was determined. There were 14 Control Subjects and 6 Zephyr EBV Subjects that had no treatment and no follow-up at 30-days or later, leaving 87 of 101 Control Subjects and 214 of 220 Zephyr EBV Subjects for safety analysis. Subjects who had one or more of these events during study follow-up were considered to have experienced an MCC on the date of the first such adverse event to occur. The Major Complications Composite (MCC) consisted of the events listed in the following table.

Table 44 Components of the Major Complications Composite (MCC)

Death, all-cause
Empyema
Massive hemoptysis resulting in respiratory failure or blood loss > 300cc in ≤ 24hr
Pneumonia distal to the implanted valves
Pneumothorax or prolonged air leak > 7 days
Respiratory failure on mechanical ventilation for > 24 hours

Source: P070025, September 21, 2007, Volume 011, Page 199

Eighteen (18) MCC events occurred in a total of 14 VENT Pivotal Trial subjects. One or more MCCs occurred in 1.2% of Control Subjects and in 6.1% of Zephyr EBV Subjects (p = 0.0748).

Death occurred in no Control Subjects and in 6 (2.8%) Zephyr EBV Subjects (p = 0.1867). Further information on all-cause mortality is presented in Section 9.3.1, All-Cause Mortality.

No subject in either group had empyema, and 1 Zephyr EBV Subjects had massive hemoptysis. Pneumonia distal to a valve occurred in 1.4% of Zephyr EBV Subjects; an event that could not occur in Control Subjects. Prolonged pneumothorax occurred in 1.2% of Control Subjects and in 1.4% of Zephyr EBV Subjects. Respiratory failure requiring mechanical ventilation for more than 24 hours occurred in 1.2% of Control Subjects and in 1.9% of Zephyr EBV Subjects.

Table 45 Primary Safety Outcome: Major Complications Composite at 6 Months

Safety Outcome	Control % (n / N)	Zephyr EBV % (n / N)	Delta (95% CI) [1]	p value [2]
MCCs at 6 months	1.2% (1 / 87)	6.1% (13 / 214)	4.9% (1.0, 8.8)	0.0748
Death, all-cause	0.0% (0 / 87)	2.8% (6 / 214)	2.8% (0.6, 5.0)	0.1867
Empyema	0.0% (0 / 87)	0.0% (0 / 214)	--	--
Massive hemoptysis	0.0% (0 / 87)	0.5% (1 / 214)	0.5% (−0.5, 1.4)	1.0000
Distal pneumonia	--	1.4% (3 / 214)	--	--
Prolonged pneumothorax	1.2% (1 / 87)	1.4% (3 / 214)	0.3% (−2.5, 3.0)	1.0000
Respiratory failure > 24 hours	1.2% (1 / 87)	1.9% (4 / 214)	0.7% (−2.2, 3.6)	1.0000

[1] Fisher's exact 95% confidence interval
[2] Two-sided Fisher's exact test
Source: Attachment 3, Amended Statistical Analysis Report, Table 16:4

Clinical narratives for each of the subjects experiencing one or more MCCs during the VENT Pivotal Trial follow-up are contained in Appendix 7-5-9, Adverse Event Narratives for Selected Subjects.

Table 46 Summary: Subjects with One or More MCCs

	Group	MCC Event(s)	Onset (days) [1]
	Zephyr EBV	Pneumothorax > 7 days	44
	Zephyr EBV	Pneumonia distal to valve	270

Group	MCC Event(s)	Onset (days) [1]
Zephyr EBV	Respiratory failure > 24 hours Death (ischemic colitis)	54 60
Control	Death (respiratory failure)	230
Zephyr EBV	Pneumonia distal to valve	212
Zephyr EBV	Pneumothorax > 7 days	12
Zephyr EBV	Massive hemoptysis Death (massive hemoptysis)	31 48
Zephyr EBV	Death (hepatic cancer)	154
Zephyr EBV	Pneumonia distal to valve	15
Zephyr EBV	Pneumothorax > 7 days Respiratory failure > 24 hours	217 222
Zephyr EBV	Death (respiratory failure)	161
Zephyr EBV	Pneumothorax > 7 days	47
Zephyr EBV	Respiratory failure > 24 hours Death ("severe emphysema")	122 148
Zephyr EBV	Respiratory failure > 24 hours Death (metastatic cancer)	85 293
Zephyr EBV	Pneumonia distal to valve	222
Zephyr EBV	Pneumonia distal to valve	363
Control	Pneumothorax > 7 days Respiratory failure > 24 hours Death (post biopsy pneumothorax)	165 180 207
Zephyr EBV	Respiratory failure > 24 hours Death (respiratory failure)	84 133
Zephyr EBV	Respiratory failure > 24 hours	334
Zephyr EBV	Pneumonia distal to valve	179
Control	Respiratory failure > 24 hours	317
Zephyr EBV	Pneumonia distal to valve	243
Zephyr EBV	Pneumonia distal to valve	296
Zephyr EBV	Pneumonia distal to valve	20 [2]
Control	Death (lung cancer)	212
Zephyr EBV	Death (pneumonia)	248

er randomization

[2] Date of onset was reported by site as Unknown. Earliest possible onset date was the date of the EBV procedure, which was 20 days post-randomization

Source: Attachment 3, Amended Statistical Analysis Report, Table 16:1

9.3 Major Complications Composite: Related Analyses

9.3.1 All-Cause Mortality

Equivalent outcomes for all-cause mortality through 1 year were demonstrated by Kaplan-Meier analysis. There were 8 (3.7% of 214) deaths in the Zephyr EBV Subjects

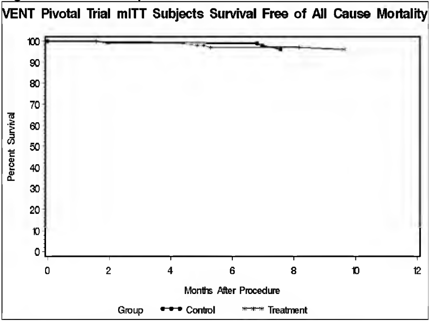
and 3 (3.5% of 87) deaths in the Control Subjects. There was no difference in the survival curves for the Control Subjects and Zephyr EBV Subjects (96.3% and 96.0% freedom from all-cause mortality respectively, p = 0.8763, log rank test).

Table 47 Survival Estimates and 95% Confidence Limits through 1 Year for Zephyr EBV and Control Subjects (M-ITT)

Treatment Group	Month	Subjects Remaining	Proportion Surviving	Lower 95% CL	Upper 95% CL
Control	0	87	1	--	--
	1	87	1	--	--
	3	84	1	--	--
	6	84	1	--	--
	12	42	0.9625	0.9209	1.0000
Zephyr EBV	0	214	1	--	--
	1	212	1	--	--
	3	202	0.9904	0.9772	1.0000
	6	194	0.9706	0.9475	0.9937
	12	115	0.9603	0.9333	0.9873

Source: Attachment 3, Amended Statistical Analysis Report, Table 17:4

Figure 7 Chart: Kaplan-Meier Curves for Freedom from All-Cause Mortality



Source: Attachment 3, Amended Statistical Analysis Report, Figure 17:2

9.3.2 Cox Regression Analysis of MCCs through Six Months

A multivariate Cox regression was performed to evaluate the impact of relevant covariates on the rate of occurrence of at least one MCC through 6 months. While there

was a trend towards a greater likelihood for MCCs at 6 months in the Zephyr EBV Subjects (hazard ratio 3.0, 95% CI = 0.7 to 13.1), this trend was not significant (p = 0.1437).

9.3.3 MCCs by Time Period through 1 Year

The rate of occurrence of MCCs during the second 6 months of follow-up demonstrated an equivalent rate of MCCs in Control Subjects (4.6%) compared with Zephyr EBV Subjects (4.7%). Control Subjects had a 3.5% mortality rate during this period compared with Zephyr EBV Subjects (0.9%). No subjects had empyema or massive hemoptysis. Pneumonia distal to a valve occurred in 2.8% of Zephyr EBV Subjects. One Zephyr EBV Subject had a pneumothorax lasting more than 7 days, and there was an equivalent rate of prolonged respiratory failure, 1.2% in Control Subjects and 0.9% in Zephyr EBV Subjects.

Table 48 Major Complication Composite for First and Second 6-Month Time Periods

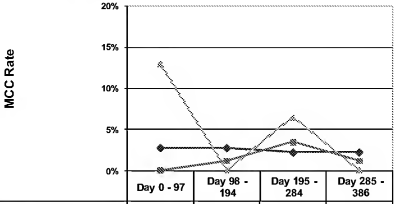
MCCs by Time Period	0 – 194 Days		195 – 386 Days	
	Control % (n / N)	Zephyr EBV % (n / N)	Control % (n / N)	Zephyr EBV % (n / N)
MCCs	1.2% (1 / 87)	6.1% (13 / 214)	4.6% (4 / 87)	4.7% (10 / 214)
Death	0.0% (0 / 87)	2.8% (6 / 214)	3.5% (3 / 87)	0.9% (2 / 214)
Empyema	0.0% (0 / 87)	0.0% (0 / 214)	0.0% (0 / 87)	0.0% (0 / 214)
Massive hemoptysis	0.0% (0 / 87)	0.5% (1 / 214)	0.0% (0 / 87)	0.0% (0 / 214)
Distal pneumonia	--	1.4% (3 / 214)	--	2.8% (6 / 214)
Pneumothorax	1.2% (1 / 87)	1.4% (3 / 214)	0% (0 / 87)	0.5% (1 / 214)
Respiratory failure > 24 hours	1.2% (1 / 87)	1.9% (4 / 214)	1.2% (1 / 87)	0.9% (2 / 214)

Source: Attachment 3, Amended Statistical Analysis Report, Tables 16:10 & 16:11

9.3.4 MCCs by Valve Removal Status through One Year

The MCC rates in the Treatment with No Valve Removals group and the Treatment with Valve Removals group decline through the one-year follow-up (see Figure 8). The overall decline in MCC rates appears to be independent of valve removals. The Zephyr EBV Treatment Subjects experienced MCCs at the same rate as Control Subjects in the second, six-month period.

Figure 8 Chart: MCC Rates by Valve Removal by Quarter



	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx- No Removals, n=183	2.7%	2.7%	2.2%	2.2%
Tx With Removals, n=31	12.9%	0.0%	6.5%	0.0%
Control, n=87	0.0%	1.2%	3.5%	1.2%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:3

9.4 Summary: Primary Safety Outcome

At 6 months of follow-up, Control Subjects had a 1.2% (1 / 87) rate of MCCs compared to Zephyr EBV Subjects who had a 6.1% (13 / 214) rate of MCCs, a difference that was not significant (p = 0.0748, Fisher's exact test). This difference was primarily driven by a trend to greater 6 month mortality in the Zephyr EBV Subjects with 6 deaths: 3 from respiratory failure, one from cancer, one from ischemic colitis and 1 from massive hemoptysis, of which only the death from hemoptysis was related to the device.

All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects (p = 0.8763, log rank test).

In the second six months of follow-up, the MCC rate in Zephyr EBV Subjects (4.7%) and the MCC rate in Control Subjects (4.6%) were almost identical. Over all 12 months of follow-up, the MCC rate for Control Subjects (4.6%) and for Zephyr EBV Subjects (10.3%) were not significantly different (p = 0.1724, Fisher's exact test).

A Cox regression analysis was done to evaluate the impact of covariates on the occurrence of at least one MCC in the 180 day window. No covariates survived the final model and Zephyr EBV Treatment was not significantly associated with MCC at 6 months (p = 0.1437).

The Primary Safety Outcome—the rate of Major Complication Composite events at 6 months—was higher but not significantly so in the Zephyr EBV Subjects (6.1%) compared with Control Subjects (1.2%, p = 0.0748).

10.0 ADDITIONAL PRE-SPECIFIED ANALYSES

10.1 Introduction

A variety of pre-specified analyses were performed for effectiveness and safety outcome measures, as well as several subgroup analyses. These include:

- 10.2. Pre-Specified Outcome Analyses
  - 10.2.1. Percent Change in Residual Volume
  - 10.2.2. Percent Change in Diffusing Capacity
  - 10.2.3. Change in Quality of Wellbeing
  - 10.2.4. Change in BODE Index
  - 10.2.5. Technical Success
  - 10.2.6. Rehospitalization
- 10.3. Pre-Specified, Analysis-Plan-Generated Subgroup Analyses
  - 10.3.1. Heterogeneity Score ≥ 15% FEV_1 and 6MWT Outcomes
  - 10.3.2. Technical Success and FEV_1
  - 10.3.3. Complete Fissure Integrity and FEV_1
- 10.4. Summary: Additional Pre-Specified Analyses

10.2 Pre-Specified Outcome Analyses

Additional pre-specified analyses on study outcomes included percent change in residual volume and diffusing capacity (DL_{CO}) and change in the BODE Index and the Quality of Well Being Scale using the CC population. The rates of rehospitalization were also analyzed.

10.2.1 Percent Change in Residual Volume

Residual volume was measured at baseline and at 180 day follow-up. There was no significant difference in the percent change in the Zephyr EBV Subjects (–1.3%) and the Control Subjects (+ 0.7%) ($p = 0.40$).

Table 49 Percent Change in Residual Volume

Residual Volume % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta[1] (95% CI)	p value [2]
Completed Cases	0.69 (21.95) 74 −2.27 (−44.2, 124.7)	−1.29 (19.83) 176 −1.03 (−63.1, 65.8)	1.25 (−5.1, 3.64)	0.4051

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:38

10.2.2 Percent Change in Diffusing Capacity

Diffusing capacity (DL_{CO}) was measured at baseline and at 180 day follow-up. There was no significant difference in the median percent change in the Zephyr EBV Subjects (+ 2.1%) and the Control Subjects (- 2.1%) (p = 0.14).

Table 50 Percent Change in Diffusing Capacity (DL_{CO})

Diffusing Capacity % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Completed Cases	−2.12 (17.45) 75 −1.69 (−85.6, 30.4)	1.81 (19.07) 178 1.05 (−46.8, 59.4)	2.74 (−2.31, 6.67)	0.1391

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:38

10.2.3 Change in Quality of Wellbeing

The Quality of Wellbeing (QWB) instrument was assessed at baseline and at 180 day follow-up. There was no measurable difference in the QWB scales between the Completed Cases Zephyr EBV Subjects and Control Subjects.

Table 51 Quality of Well Being Scale

QWB Scale Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Completed Cases	−0.02 (0.10) 71 −0.01 (−0.3, 0.3)	−0.01 (0.11) 173 0.00 (−0.4, 0.2)	0.01 (−0.01, 0.04)	0.1696

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:38

10.2.4 Change in BODE Index

The BODE Index was assessed at baseline and at 180 day follow-up. The BODE Index significantly improved (0.21 score point reduction) in the Zephyr EBV Subjects compared to the worsened results (0.32 score point increase) in the Control Subjects (p = 0.0024).

Table 52 Change in BODE Index

	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
BODE Index Change from Baseline	0.32 (1.07) 59 0.00 (−3.0, 3.0)	−0.21 (1.25) 160 0.00 (−4.0, 3.0)	−0.0 (−1.00, −0.00)	**0.0024**

[1] Difference of medians and non-parametric confidence interval
[2] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:38

10.2.5 Technical Success

Technical Success, defined for Zephyr EBV Subjects only, required target lobe exclusion confirmed clinically and by HRCT scan at 6 months. Of the 194 imaging-evaluable Zephyr EBV Subjects at 6 months, 56.2% (109 / 194, 95% CI 48.9, 63.3%) demonstrated HRCT-confirmed exclusion of the target lobe by the Zephyr EBV devices at 6 months. The failure modes for the 85 subjects with HRCT-determined Technical Failure are tabulated below.

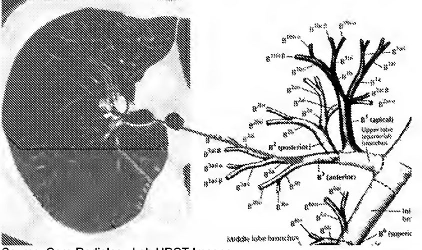
Table 53 Reasons for Incomplete Lobar Exclusion on 180 Day HRCT

Zephyr EBV Group		**% (n)**
HRCT (180 Day) Determined Incomplete Lobar Exclusion		100.0% (85)
Occurring at procedure and determined by site	Segment too small for valve	3.5% (3)
	Unable to place valve	4.7% (4)
	Side branch airway too small	1.2% (1)
	Unable to valve apical segment	2.3% (2)
Occurring at procedure and determined by HRCT	Valve(s) in place but not fully occlusive	78.8% (67)
Occurring post-procedure due to migration, expectoration or removal	Valve(s) removed and not replaced	4.7% (4)
	Valve(s) migrated, removed and not replaced	2.3% (2)
	Valve(s) expectorated and not replaced	2.3% (2)

Source: P070025, September 21, 2007, Volume 011, Page 103

Figure 9 demonstrates the most common reason for Technical Failure, which is a valve which is in place but not fully occlusive. Here, the valve target is RUL B3, but the distal end of valve is in B3a leaving B3b exposed.

Figure 9 Picture: HRCT Image Example of Non-Lobar Exclusion (Technical Failure)



Source: Core Radiology Lab HRCT Images.

10.2.6 Rehospitalization

The rates of rehospitalization for any cause through 6 months of study follow-up were 16.1% (14 / 87) of Control Subjects and 27.1% (58 / 214) of Zephyr EBV Subjects (p = 0.0522). From the 6-month follow up to 1 year, Control Subjects had a 12.6% (11 / 87) rate of rehospitalization versus 19.6% (42 / 214) for Zephyr EBV Subjects (p = 0.1823).

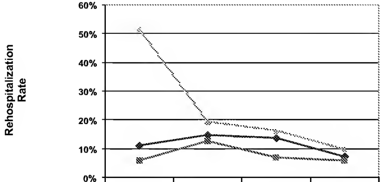
Table 54 Rehospitalization Rates through 6 and 12 Months

Rehospitalization	Control Subjects % (n / N)	Zephyr EBV Subjects	Risk Ratio (95% CI)	p value [1]
Through 6 Months	16.1 (14 / 87)	27.1 (58 / 214)	1.7 (1.0, 2.9)	0.0522
From 6 to 12 Months	12.6 (11 / 87)	19.6 (42 / 214)	1.6 (0.8, 2.9)	0.1823

[1] Two-tailed Fisher's exact test
Source: Attachment 3, Amended Statistical Analysis Report, Table 18:9

Rehospitalization rates were higher in Zephyr EBV Subjects early in the follow-up, declining to a rate similar to Control Subjects in the fourth quarter after randomization. The chart below shows the rate of rehospitalizations by quarter, separating out the potentially confounding effect of valve removals. The higher Rehospitalization Rate in Zephyr EBV Subjects in the first quarter was associated with valve removals.

Figure 10 Chart: Per-Subject Rehospitalization Rates by Quarter



	Day 0 - 97	Day 98 -194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	10.9%	14.8%	13.7%	7.1%
Tx - With Removals, n=31	51.6%	19.4%	16.1%	9.7%
Control, n=87	5.8%	12.6%	6.9%	5.8%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:1.

10.3 Pre-Specified, Analysis-Plan-Generated Subgroup Analyses

The VENT Pivotal Trial documents pre-specified a subgroup analysis on Technical Success, and for independent predictor variables which were retained in the multivariate model (see Section 4.5.6). These two remaining significant covariates were Heterogeneity Score and Fissure Integrity. All subgroup analyses are reported using the Completed Cases population.

10.3.1 Technical Success, FEV_1 and 6MWT Outcomes

Zephyr EBV Subjects with Technical Success (HRCT-confirmed target lobe exclusion at 6 months) had a greater mean percent change in FEV_1 at 6 months (9.4%) than those without Technical Success (0.1%) ($\Delta = 9.4\%$, $p = 0.0009$). Technical Success did not have a significant impact on percent change in 6MWT at 6 Months ($p = 0.6746$).

Table 55 FEV$_1$ and 6MWT: Treatment Group Only—Effect of Lobar Exclusion on % Change in Primary Outcomes 6 Months (CC)

CC Subjects	No Technical Success Mean (SD) N Median (Min, Max)	Technical Success Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
FEV$_1$ (%)	0.1 (14.9) 77 −1.3 (−38.3, 40.0)	9.4 (21.9) 100 5.5 (−28.7, 78.9)	9.4 [1] (3.9, 14.8)	**0.0009** [2]
6MWT (%)	3.3 (21.6) 77 3.0 (−53.9, 66.2)	5.2 (23.7) 99 3.9 (−83.3, 108.0)	0.9 [3] (−4.0, 6.9) [4]	0.6746 [5]

[1] Difference of means and unequal variance t-test confidence interval (9.4 - 0.1 = 9.4 due to rounding).
[2] One-sided unequal variance t-test
[3] Difference of medians
[4] Non-parametric confidence interval
[5] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:33

10.3.2 Heterogeneity Score ≥ 15%, FEV$_1$ and 6MWT Outcomes

The Heterogeneity Score measured the difference in disease severity between ipsilateral lobes of the lung, calculated as the difference in percentage destruction (Density Score) as determined by HRCT. (Please refer to Section 4.6.4 for details). The median baseline value for Heterogeneity Score (15%) was chosen as the threshold for the high heterogeneity subgroup. Higher Heterogeneity as a predictor of Zephyr EBV treatment response is consistent with the hypothesized mechanism of action of lung volume reduction, which reduces non-ventilating space and increases the ventilation of the remaining healthy lung parenchyma. Subjects with High Heterogeneity have less destruction and thus more potentially expandable lung parenchyma in the non-treated lobe compared with subjects with less heterogeneous emphysema, and would tend to respond better.

In the pre-specified multivariate, mixed model analysis, Heterogeneity Score remained in both FEV$_1$ and 6MWT models.

Analysis of the co-primary effectiveness outcomes for study subjects with High Heterogeneity Scores ($\geq$ 15%) revealed an improved response for unilateral Zephyr EBV treatment compared with all study subjects, consistent with the physiologic rationale of this treatment. The percent changes in the co-primary outcomes for the Completed-Cases High-Heterogeneity Subgroup were:

FEV$_1$: Controls: −2.2%: Zephyr EBV: +10.1% (Δ = +12.3%, $p < 0.0001$)
6MWT: Controls: −5.9%: Zephyr EBV: +7.3% (Δ = +14.4%, $p = 0.0003$)

Table 56 Subgroup Analysis: Percent Change in FEV_1 and 6MWT in High Heterogeneity Subgroup at 6 Months (CC)

High Heterogeneity Subgroup Analysis	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)	p value
FEV_1 CC	−2.2 (11.3) 40 −4.2 (−21.0, 25.5)	10.1 (22.3) 91 7.5 (−38.3, 78.9)	12.3 [1] (6.5, 18.1)	<0.0001 [2]
6MWT CC	−5.9 (21.9) 38 −7.6 (−54.9, 66.7)	7.3 (26.6) 90 6.8 (−83.3, 108.0)	14.4 [3] (6.3, 21.0) [4]	0.0003 [5]

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
[3] Difference of medians
[4] Non-parametric confidence interval
[5] One-sided Wilcoxon rank-sum test
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:11

10.3.3 Complete Fissure Integrity and FEV_1

Fissure Integrity was assessed by HRCT as a radiological proxy for interlobar collateral airflow. Completeness of the interlobar fissure as a predictor of Zephyr EBV treatment response is consistent with the hypothesized mechanism of action of lung volume reduction, as a complete fissure would result in greater volume reduction in the treated lobe due to isolation from unwanted collateral air movement.

In the pre-specified multivariate, mixed model analysis, Fissure Integrity remained as a significant interaction with Zephyr EBV treatment for % change in FEV_1 at six months.

The percent changes in FEV_1 for the Completed-Cases Complete Interlobar Fissure Subgroup were:

FEV_1: Controls: −2.7%: Zephyr EBV: +13.5% ($\Delta = +16.2\%$, $p < 0.0001$)

Table 57 Subgroup Analysis: Percent Change in FEV_1 by Fissure Integrity at 6 Months

% Change in FEV_1	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)	p value [2]
Complete Interlobar Fissure (CC)	−2.7 (10.2) 33 −3.7 (−21.0, 25.5)	13.5 (22.9) 68 9.5 (−28.7, 78.9)	16.2 (9.65, 22.76) [1]	<0.0001

[1] Difference of means and unequal variance t-test confidence interval
[2] One-sided unequal variance t-test
Source: Appendix 7-5-8, Statistical Analysis of the VENT Trial, Table 25:14

10.4 Summary: Additional Pre-Specified Analyses

Additional effectiveness analyses were performed for residual volume, diffusing capacity, Quality of Wellbeing and the BODE Index. Although Zephyr EBV Subjects trended higher in all these measures, only the BODE Index showed an improvement that was significant ($p = 0.0024$).

Technical Success (complete lobar exclusion by HRCT at 6 months) was achieved in 56.2% of Zephyr EBV Subjects, with the majority of Technical Failures (77.8%) occurring when one or more valves were found to be in place but not fully occlusive.

Rehospitalization rates through 6 months were 16.1% for Control Subjects and 27.1% for Zephyr EBV Subjects, a difference that bordered on significant ($p = 0.0522$). For the period from 6 to 12 months, this difference began to converge, with 12.6% for Control Subjects and 19.6% for Zephyr EBV Subjects. Most of this difference occurred during the first quarter of follow-up in subjects who required removal of one or more Zephyr valves.

Technical Success subjects had an FEV_1 improvement that was 9.4 percentage points higher in subjects with Technical Success compared with subjects with Technical Failure ($p = 0.0009$).

High Heterogeneity subjects demonstrated a substantially larger therapeutic benefit compared with the study population as a whole: FEV_1 improvement at 6 months was 12.3 percentage points higher ($p < 0.0001$), and 6MWT at 6 months was 14.4 percentage points higher ($p = 0.0003$), in High Heterogeneity Zephyr EBV Subjects compared with High Heterogeneity Control Subjects.

Subjects with Complete Fissure Integrity had an FEV_1 improvement that was 16.2 percentage points higher than subjects with Incomplete Fissure Integrity ($p < 0.0001$).

11.0 RESPONDER ANALYSES

11.1 Introduction

Responder analyses were performed on several effectiveness outcome measures to further explore the clinical importance of the observed changes. These further analyses were only performed on those outcome measures that had been found to be statistically significant on pre-specified hypothesis testing.

Responder analyses dichotomize the change in an outcome measure at a level of clinical importance and then compare the proportion of "clinically important" responders in each group. The level of clinical importance—often termed minimal clinically important difference, or MCID—is best established prior to the investigation, either based on empirically determined estimates or clinically accepted values, but when analyzed *post hoc*, MCIDs should be based on independent, empirically determined values whenever possible.

This type of analysis allows the clinician and patient to estimate the treatment effect that an individual is likely to experience. The analysis is quite similar to calculating odds ratios, relative rates and "number needed to treat". All four of these are well-established methods to analyze and convey anticipated clinical treatment effect for individuals for outcome measures that have already been established as statistically significantly improved.[25 - 30]

- 11.2. Responder Analyses: FEV_1
  - 11.2.1. Subjects with Maintained FEV_1
  - 11.2.2. High Heterogeneity Subjects with Maintained FEV_1
  - 11.2.3. Subjects with $\geq$ 15% Improvement in FEV_1
  - 11.2.4. High Heterogeneity Subjects with $\geq$ 15% Improvement in FEV_1
- 11.3. Responder Analyses: 6MWT
  - 11.3.1. Subjects with Maintained 6MWT
  - 11.3.2. High Heterogeneity Subjects with Maintained 6MWT
  - 11.3.3. Subjects with $\geq$ 15% Improvement in 6MWT
  - 11.3.4. High Heterogeneity Subjects with $\geq$ 15% Improvement in 6MWT
- 11.4. Responder Analyses: Other Effectiveness Outcome Measures
  - 11.4.1. Subjects with $\geq$ 8 Point Improvement in SGRQ
  - 11.4.2. Subjects with $\geq$ 1 Point Improvement in mMRC
  - 11.4.3. Subjects with $\geq$ 10 Watt Improvement in Maximum Workload during Cycle Ergometry

11.2 Responder Analyses: FEV_1

Two pre-specified responder analyses for FEV_1 were performed using percentage change values: one with subjects who maintained FEV_1 without loss (i.e. change of ≥ 0%) and one with subjects who showed ≥ 15% improvement.

11.2.1 Subjects with Maintained FEV_1

The proportion of Completed-Cases Zephyr EBV Subjects with maintained FEV_1 (change from baseline ≥ 0%) at 6 months was 58.7% (105 / 179) compared with Control Subjects (41.3%, 31 / 75).

Zephyr EBV Subjects were 1.4 times more likely than Control Subjects to maintain their FEV_1 through 6 months of follow-up (95% CI 1.1 – 1.9).

Table 58 Responder Analysis: Subjects with Maintained FEV_1 (Increase ≥ 0%) at 6 Months (CC)

Increase ≥ 0% in FEV_1	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	41.3 (31 / 75)	58.7 (105 / 179)	1.4 (1.1, 1.9)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.2.2 High Heterogeneity Subjects with Maintained FEV_1

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with maintained FEV_1 (change from baseline ≥ 0%) at 6 months was 65.9% (60 / 91) compared with Control Subjects (32.5%, 13 / 40).

Zephyr EBV Subjects were 2.0 times more likely than Control Subjects to maintain their FEV_1 through 6 months of follow-up (95% CI 1.3 – 3.2).

Table 59 Responder Analysis: High Heterogeneity Subjects with Maintained FEV_1 at 6 Months (CC)

Increase ≥ 0% in FEV_1	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
High Heterogeneity Subjects	32.5 (13 / 40)	65.9 (60 / 91)	2.0 (1.3, 3.2)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:19

11.2.3 Subjects with ≥ 15% Improvement in FEV_1

The proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in FEV_1 from baseline to 6 months was 23.5% (42 / 179) compared with Control Subjects (10.7%, 8 / 75).

Zephyr EBV Subjects were 2.2 times more likely than Control Subjects to improve their FEV_1 by ≥ 15% through 6 months of follow-up (95% CI 1.1 – 4.5).

Table 60 Responder Analysis: Subjects with FEV_1 Improvement ≥ 15% at 6 Months (CC)

Increase ≥ 15% in FEV_1	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	10.7 (8 / 75)	23.5 (42 / 179)	2.2 (1.1, 4.5)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.2.4 High Heterogeneity Subjects with ≥ 15% Improvement in FEV_1

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in FEV_1 from baseline to 6 months was 35.2% (32 / 91) compared with Control Subjects (12.5%, 5 / 40).

Zephyr EBV Subjects in the High Heterogeneity Subgroup were 2.8 times more likely than Control Subjects to improve their FEV_1 by ≥ 15% through 6 months of follow-up (95% CI 1.2 – 6.7).

Table 61 Responder Analysis: High Heterogeneity Subjects with FEV_1 Improvement ≥ 15% at 6 Months (CC)

Increase ≥ 15% in FEV_1	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
High Heterogeneity Subjects	12.5 (5 / 40)	35.2 (32 / 91)	2.8 (1.2, 6.7)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:19

11.3 Responder Analyses: 6MWT

Two pre-specified responder analyses for 6MWT were performed using percentage change values: one with subjects who maintained 6MWT without loss (i.e. change of ≥ 0%) and one with subjects who showed ≥ 15% improvement.

11.3.1 Subjects with Maintained 6MWT

The proportion of Completed-Cases Zephyr EBV Subjects with maintained 6MWT (change from baseline ≥ 0%) from baseline to 6 months was 60.7% (108 / 178) compared with Control Subjects (46.6%, 34 / 73).

Zephyr EBV Subjects were 1.3 times more likely than Control Subjects to maintain their 6MWT through 6 months of follow-up (95% CI 1.0 – 1.7).

Table 62 Responder Analysis: Subjects with Maintained 6MWT (Increase ≥ 0%) at 6 Months (CC)

Increase ≥ 0% in 6MWT	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	46.6 (34 / 73)	60.7 (108 / 178)	1.3 (1.0, 1.7)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.3.2 High Heterogeneity Subjects with Maintained 6MWT

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with maintained 6MWT (change from baseline ≥ 0%) from baseline to 6 months was 65.6% (59 / 90) compared with Control Subjects (36.8%, 14 / 38).

Zephyr EBV Subjects were 1.8 times more likely than Control Subjects to maintain their 6MWT through 6 months of follow-up (95% CI 1.1 – 2.8).

Table 63 Responder Analysis: High Heterogeneity Subjects with Maintained 6MWTat 6 Months (CC)

Increase ≥ 0% in 6MWT	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
High Heterogeneity Subjects	36.8 (14 / 38)	65.6 (59 / 90)	1.8 (1.1, 2.8)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:19

11.3.3 Subjects with ≥ 15% Improvement in 6MWT

The proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in 6MWT from baseline to 6 months was 25.3% (45 / 178) compared with Control Subjects.(17.8%, 13 / 73).

Zephyr EBV Subjects were 1.4 times more likely than Control Subjects to improve their 6MWT by ≥ 15% through 6 months of follow-up (95% CI 0.8 – 2.5).

Table 64 Responder Analysis: Subjects with Major Improvement (≥ 15%) in 6MWT at 6 Months (CC)

Increase ≥ 15% in 6MWT	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	17.8 (13 / 73)	25.3 (45 / 178)	1.4 (0.8, 2.5)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.3.4 High Heterogeneity Subjects with ≥ 15% Improvement in 6MWT

In the High Heterogeneity Subgroup, the proportion of Completed-Cases Zephyr EBV Subjects with ≥ 15% improvement in 6MWT from baseline to 6 months was 31.1% (28 / 90) compared with Control Subjects (13.2%, 5 / 38).

Zephyr EBV Subjects in the High Heterogeneity Subgroup were 2.4 times more likely than Control Subjects to improve their 6MWT by ≥ 15% through 6 months of follow-up (95% CI 1.0 – 5.7).

Table 65 Responder Analysis: High Heterogeneity Subjects with 6MWT Improvement ≥ 15% at 6 Months (CC)

Increase ≥ 15% in 6MWT	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
High Heterogeneity Subjects	13.2 (5 / 38)	31.1 (28 / 90)	2.4 (1.0, 5.7)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:19

11.4 Responder Analyses: Other Effectiveness Outcome Measures

Four other effectiveness outcome measures were statistically significantly improved in the Zephyr EBV Subjects group: SGRQ, mMRC, maximum workload during cycle ergometry and BODE Index. Each of these outcome measures was subjected to responder analysis using established MCID levels to further assess the clinical importance of the observed treatment effect.

11.4.1 Subjects with ≥ 8 Point Improvement in SGRQ Score

A responder analysis was performed on the proportion of Completed-Cases Subjects with significant improvement in SGRQ from baseline to 6 months. The analysis was performed using ≥ 8 points improvement (≤ –8 point decline) was used based on the MCID value used in the NETT trial for lung volume reduction surgery.[2]

The proportion of Zephyr EBV Subjects with ≥ 8 point improvement in SGRQ was 31.0% (49 / 158) compared with Control Subjects (11.3%, 7 / 62).

Zephyr EBV Subjects were 2.7 times more likely than Control Subjects to improve their SGRQ by ≥ 8 points through 6 months of follow-up (95% CI 1.3 – 5.7).

Table 66 Responder Analysis: Subjects with SGRQ Improvement of ≥ 8 Points at 6 Months (CC)

Improvement ≥ 8 Points in SGRQ	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	11.3 (7 / 62)	31.0 (49 / 158)	2.8 (1.3, 5.7)

Source: Attachment 3, Amended Statistical Analysis Report Table 25:16

11.4.2 Subjects with ≥ 1 Point Improvement in mMRC Dyspnea Scale

A responder analysis was performed on the proportion of Completed-Cases Subjects with significant improvement in mMRC from baseline to 6 months. There is no clear MCID established in the literature based on empirical evidence.[27] An MCID of ≥ 1 point (≤ –1 point decline) was used, for three reasons. First, the mMRC Dyspnea Scale has only 5 categories, scored 0 – 4, and thus the smallest difference a subject can score is 1 point. Secondly, a similar dyspnea scale, the Transition Dyspnea Index, has a recommended MCID of 1 point.[27] Thirdly, the use of ½ the standard deviation of an outcome measure as an estimated MCID has been recommended;[32-35] the VENT Pivotal Study baseline mMRC scores had a ½ standard deviation of 0.42, and the dichotomization of study subjects was the same whether 0.42 or 1 was used because of the integer nature of the scoring.

The proportion of Zephyr EBV Subjects with ≥ 1 point improvement in the mMRC Scale Index was 29.0% (47 / 162) compared with Control Subjects (16.4%, 11 / 67).

Zephyr EBV Subjects were 1.8 times more likely than Control Subjects to improve their mMRC score by ≥ 1 point through 6 months of follow-up (95% CI 1.0 – 3.2).

Table 67 Responder Analysis: Subjects with mMRC Dyspnea Scale Improvement of ≥ 1 Point at 6 Months (CC)

Improved ≥ 1 Point in mMRC	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	16.4 (11 / 67)	29.0 (47 / 162)	1.8 (1.0, 3.2)

Source: Attachment 3, Amended Statistical Analysis Report Table 25:16

11.4.3 Subjects with ≥ 10 Watt Improvement in Maximum Workload during Cycle Ergometry

A responder analysis was performed on the proportion of Completed Cases Subjects with significant improvement in Maximum Workload during Cycle Ergometry from baseline to 6 months. The MCID level used was 10 watts, based on the published assessments of the NETT cohort.[2, 36]

The proportion of Completed Cases Zephyr EBV Subjects with ≥ 10 watt improvement in Maximum Workload during Cycle Ergometry was 24.7% (41 / 166) compared with Control Subjects (13.0%, 9 / 69)

Zephyr EBV Subjects were 1.9 times more likely than Control Subjects to show a ≥ 10 watt improvement in Maximum Workload during Cycle Ergometry through 6 months of follow-up (95% CI 1.0 – 3.7).

Table 68 Responder Analysis: Subjects with Improvement in Maximum Workload during Cycle Ergometry ≥ 10 Watts at 6 Months (CC)

Increase ≥ 10 watts in max workload	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	13.0 (9 / 69)	24.7 (41 / 166)	1.9 (1.0, 3.7)

Source: Attachment 3, Amended Statistical Analysis Report, Table 25:16

11.4.4 Subjects with ≥ 1 Point Improvement in the BODE Index

A responder analysis was performed on the proportion of Completed Cases Subjects with significant improvement in the BODE Index from baseline to 6 months. The MCID level used was 1 unit, based on the studies of Celli and Martinez.[37, 38]

The proportion of Zephyr EBV Subjects with ≥ 1 point improvement (≤ –1 point decline) in the BODE Index was 40.0% (64 / 160) compared with that of Control Subjects (18.6%, 11 / 59).

Zephyr EBV Subjects were 2.2 times more likely than Control Subjects to show a ≥ 1 point improvement (≤ –1 point decline) in the BODE Index through 6 months of follow-up (95% CI 1.2 – 3.8).

**Table 69 Responder Analysis:
Subjects with ≥ 1 Point Improvement in the BODE Index at 6 Months (CC)**

Improvement ≥ 1 Point in BODE	Control % (n / N)	Zephyr EBV % (n / N)	Relative Rate (95% CI)
CC Subjects	18.6 (11 / 59)	40.0 (64 / 160)	2.2 (1.2, 3.8)

Source: Attachment 3, Amended Statistical Analysis Report Table 25:17.

11.5 Summary: Responder Analyses

Responder analyses for the VENT Pivotal Study effectiveness measures of FEV_1 and 6MWT demonstrated that a substantially larger proportion of Zephyr EBV Subjects achieved clinically important levels of improvement than did Control Subjects.

**Table 70 Responder Analysis Summary for
Maintenance and ≥ 15% Improvement in FEV_1 and 6MWT at 6 Months**

Outcome Measure	Relative Rate (95% CI)
FEV_1 ≥ 0%	1.4 (1.1 – 1.9)
FEV_1 – High Heterogeneity Subgroup ≥ 0%	2.0 (1.3 – 3.2)
FEV_1 ≥ 15%	2.2 (1.1 – 4.5)
FEV_1 – High Heterogeneity Subgroup ≥ 15%	2.8 (1.2 – 6.7)
6MWT ≥ 0%	1.3 (1.0 – 1.7)
6MWT – High Heterogeneity Subgroup ≥ 0%	1.8 (1.1 – 2.8)
6MWT ≥ 15%	1.4 (0.8 – 2.5)
6MWT – High Heterogeneity Subgroup ≥ 15%	2.4 (1.0 – 5.7)

Source: Attachment 3, Amended Statistical Analysis Report Tables 25:16 & 25:19.

Responder analyses for the VENT Pivotal Study effectiveness measures of SGRQ, mMRC, maximum workload and the BODE Index all demonstrated that a substantially larger proportion of Zephyr EBV Subjects achieved clinically important levels of improvement than did Control Subjects (see Table 71).

Table 71 Responder Analysis Summary for Secondary Effectiveness Outcomes and BODE at 6 Months

Outcome Measure	MCID	Relative Rate (95% CI)
SGRQ	8 points	2.8 (1.3 – 5.7)
mMRC	1 point	1.8 (1.0 – 3.2)
Ergometry	10 watts	1.9 (1.0 – 3.7)
BODE Index	1 point	2.2 (1.2 – 3.8)

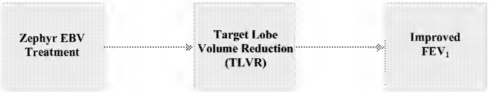
Source: Attachment 3, Amended Statistical Analysis Report Tables 25:16.

12.0 TREATMENT, VOLUME REDUCTION AND FEV_1

12.1 Introduction

Several analyses of study variables were performed in Zephyr EBV Subjects only to explore the primary rationale of Zephyr EBV treatment: that Zephyr EBV treatment leads to reduction in target lobe volume reduction (TLVR) as measured by Target Lobe Atelectasis Score (TLAS), and that this is associated with measurable therapeutic benefit as assessed by improvement in FEV_1.

Figure 11 Chart: Zephyr EBV Treatment, TLVR and FEV_1



These pre-specified analyses of factors affecting change in FEV_1 at 6 months—already demonstrated to be a significant effectiveness outcome measure—are an important exploration of Zephyr EBV performance, and help to elucidate and confirm hypothesized therapeutic mechanisms. The relationships that are examined in this section are as follows:

- 12.2. Treatment, Volume Reduction and Improved FEV_1
  - 12.2.1. Zephyr EBV Treatment Leads to TLVR
  - 12.2.2. TLVR is Significantly Associated with Improved FEV_1 at 6 Months
- 12.3. Factors Associated with Target Lobe Volume Reduction
  - 12.3.1. Technical Success and Target Lobe Volume Reduction
  - 12.3.2. Fissure Integrity and Target Lobe Volume Reduction
  - 12.3.3. Technical Success, Fissure Integrity and Target Lobe Volume Reduction
- 12.4. Other Volume Changes Assessed by HRCT
- 12.5. Factors Associated with Improved FEV_1
  - 12.5.1. Technical Success, Fissure Integrity and FEV_1
- 12.6. Discussion: Treatment, Volume Reduction and FEV_1

12.2 Treatment, Volume Reduction and Improved FEV_1

12.2.1 Zephyr EBV Treatment Leads to TLVR

Target Lobe Volume Reduction (TLVR) was assessed by Target Lobe Atelectasis Score at total lung capacity ($TLAS_{TLC}$). TLAS is a direct measure of target lobar volume change over time, calculated as the percentage difference in HRCT-assessed volume from baseline to 6 months (see Section 4.6.7).

Implantation of the Zephyr EBV in study subjects was associated with a large and highly significant difference in the $TLAS_{TLC}$ ($p < 0.0001$) at 6 months between Zephyr EBV Subjects (−20.6%) and Control Subjects (−1.7%). Thus, Zephyr EBV treatment results in dramatic volume reduction in the target lobe over time.

Table 72 Effect of EBV Treatment on $TLAS_{TLC}$

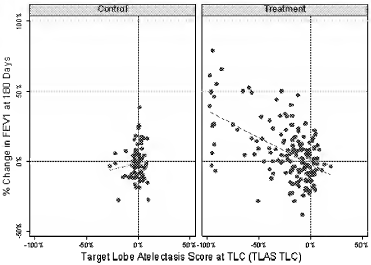
	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)
$TLAS_{TLC}$	−1.7% (7.0%) 73 −1.1% (−27.5%, 9.8%)	−20.6% (27.3%) 172 −12.2% (−97.7%, 19.3%)	−18.9 (−23.3, −14.5)

[1] Difference of means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:25

12.2.2 TLVR is Significantly Associated with Improved FEV_1 at 6 Months

Analysis of the relationship between TLVR measured by $TLAS_{TLC}$ and therapeutic benefit measured by percent change in FEV_1 at 6 months reveals a dramatic difference between Control Subjects and Zephyr EBV Subjects. Control Subjects have no significant relationship between these two variables, whereas Zephyr EBV Subjects demonstrate much more substantial reductions in $TLAS_{TLC}$ and a significant association between $TLAS_{TLC}$ and Percent Change in FEV_1 in the Zephyr EBV Subjects ($r^2 = 0.2785$, $p = 0.0000$, $n = 179$). This is dramatically demonstrated in the following chart:

Figure 12 Chart: $TLAS_{TLC}$ vs. % Change in FEV_1 (CC)



Source: Attachment 3, Amended Statistical Report Figure 13.9

12.3 Factors Associated with Target Lobe Volume Reduction

Zephyr EBV treatment is intentionally designed to produce Target Lobe Volume Reduction (TLVR). Two factors were significantly associated with TLVR, Technical Success and Fissure Integrity, both of which are clinically and physiologically expected and relevant.

12.3.1 Technical Success and Target Lobe Volume Reduction

Zephyr EBV Subjects with Technical Success (complete lobar exclusion at 6 months) as determined by HRCT had a 17.0% larger reduction in $TLAS_{TLC}$ than those with Technical Failure (incomplete lobar exclusion), respectively −28.1% vs. −11.1% ($p = 0.0001$).

Table 73 Technical Success (Complete Lobar Exclusion) and $TLAS_{TLC}$

	Technical Failure (Incomplete Lobar Exclusion) Mean (SD) N Median (Min, Max)	Technical Success (Complete Lobar Exclusion) Mean (SD) N Median (Min, Max)	Delta (95% CI) [1]
$TLAS_{TLC}$	−11.1% (14.6%) 76 -7.4% (−54.1%, 6.7%)	−28.1% (32.3%) 96 −17.6% (−97.7, 19.3%)	−17.0% (−24.3, -9.7)

[1] Unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:29

12.3.2 Fissure Integrity and Target Lobe Volume Reduction

Zephyr EBV Subjects with Fissure Integrity in the target lobe as determined by HRCT had significantly larger reductions in $TLAS_{TLC}$ compared to those with Incomplete Fissures.

For the left lung, subjects with a complete left oblique fissure had a 19.4% greater reduction in $TLAS_{TLC}$ of −40.1% compared with −20.7% for subjects with an incomplete left oblique fissure (p = 0.0111).

Table 74 Left Target Lung, Fissure Integrity and $TLAS_{TLC}$ (CC)

	Incomplete Left Oblique Fissure Mean (SD) N Median (Min, Max)	Complete Left Oblique Fissure Mean (SD) N Median (Min, Max)	Delta 95% CI [1]
$TLAS_{TLC}$	−20.7% (22.8%) 25 −11.7% (−71.0, 19.3%)	−40.1% (36.9%) 40 −27.9% (−96.1, 4.0%)	−19.4% (−34.2, −4.6)

[1] Unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 13:28

The right lung, with two fissures, is more complicated, but the same positive effect of HRCT-determined fissure integrity on the magnitude of $TLAS_{TLC}$ response is present. Subjects with both fissures complete have a significantly greater change in $TLAS_{TLC}$ of −33.0% compared to −13.3% or less if any or both of the fissures are incomplete.

Table 75 Right Target Lung, Fissure Integrity and $TLAS_{TLC}$

	$TLAS_{TLC}$ Mean (SD) N Median (Min, Max)
Both Fissures Complete	−33.0% (27.9%) 23 −25.4% (−97.7, 3.3%)
Right Horizontal-Only Complete	−13.3% (12.0%) 13 −12.6% (−36.4, 3.7%)
Right Oblique-Only Complete	−10.1% (10.1%) 24 −10.7% (−36.3, 8.6%)
Neither Fissure Complete	−4.4% (10.9%) 39 −2.6% (−37.9, 13.8%)

Source: Attachment 3, Amended Statistical Analysis Report, Table 13:27

12.3.3 Technical Success, Fissure Integrity and Target Lobe Volume Reduction

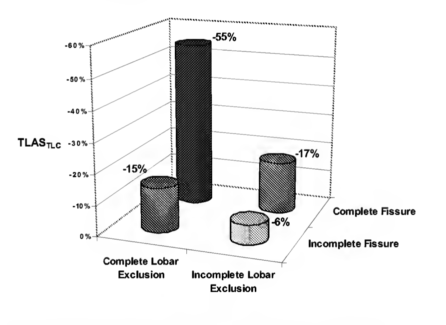
When both Technical Success and Fissure Integrity are jointly compared with change in $TLAS_{TLC}$ there is an additive effect, with Zephyr EBV Subjects with both Technical Success and Fissure Integrity having a reduction of −54.8%.

Table 76 $TLAS_{TLC}$ in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity

	Incomplete Lobar Exclusion Mean (SD) N Median (Min, Max)	Complete Lobar Exclusion Mean (SD) N Median (Min, Max)
Both Fissures Complete	−17.2% (15.3%) 29 −14.1% (−50.8, 4.0%)	−54.8% (35.8%) 34 −52.4% (−97.7, 3.9%)
One or Both Fissures Incomplete	−6.4% (10.9%) 46 −4.3% (−37.9, 6.7%)	−14.7% (18.3%) 55 −11.7% (−71.0, 19.3%)

Source: Attachment 3, Amended Statistical Analysis Report Table 13:32

Figure 13 Chart: $TLAS_{TLC}$ in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity



Source: Attachment 3, Amended Statistical Analysis Report, Table 13:32

12.4 Factors Associated with Improved FEV_1

Zephyr EBV treatment, Technical Success and Fissure Integrity were shown above to be associated with TLVR. All three of these factors were also associated with significant improvements in FEV_1 at 6 months.

Zephyr EBV Treatment: This was demonstrated as one of the two co-Primary Outcome Measures (See Section 8.2.1) where the Zephyr EBV Subjects had a 6.8% greater change in FEV_1 compared with the Control Subjects.

Technical Success: This was demonstrated as a pre-specified subgroup analysis (See Section 10.3.1) where the Zephyr EBV Subjects with Technical Success had a 9.4% greater change in FEV_1 compared with Zephyr EBV Subjects without Technical Success.

Fissure Integrity: This was demonstrated as a pre-specified subgroup analysis (See Section 10.3.3) where the Zephyr EBV Subjects with Complete Fissure Integrity had a 16.2% greater change in FEV_1 compared with Control Subjects.

12.4.1 Technical Success, Fissure Integrity and FEV_1

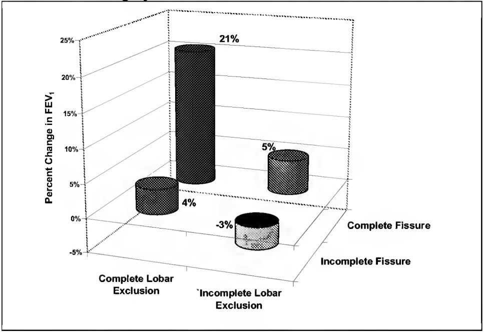
Zephyr EBV subjects with Technical Success (Complete Lobar Exclusion) and Complete Fissures have a much greater improvement in FEV_1 (+20.6%) compared to those Zephyr EBV Subjects with neither factor (−3.2%, range −38.3% to +21.4%).

Table 77 Percent Change in FEV_1 at 6 Months in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity

	Incomplete Lobar Exclusion Mean (SD) N Median (Min, Max)	Complete Lobar Exclusion Mean (SD) N Median (Min, Max)
Complete Fissures	5.2% (17.4%) 29 6.5% (−28.6, 40.0%)	20.6% (25.1%) 37 19.3% (−28.7, 78.9%)
Incomplete	−3.2% (12.4%) 47 −4.2% (−38.3, 21.4%)	3.7% (16.9%) 56 2.2% (−21.0, 52.3%)

Source: Attachment 3, Amended Statistical Analysis Report, Table 13:34

Figure 14 Chart: FEV_1 in Zephyr EBV Subjects by Lobar Exclusion and Fissure Integrity



Source: Attachment 3, Amended Statistical Analysis Report, Table 13:34

12.5 Summary: Treatment, Volume Reduction and FEV_1

The VENT Pivotal Trial prospectively assessed the hypothesized mechanism of treatment effect, which was to cause volume loss in non-ventilating lung with resulting improved ventilation in healthier lung parenchyma.

Study results strongly suggest this to be the case. Unilateral treatment of subjects with heterogeneous emphysema with Zephyr EBVs elicited substantial target lobe volume reduction (TLVR) as measured by target lobe atelectasis score ($TLAS_{TLC}$). Zephyr EBV Subjects showed a 20.6% reduction in lobar volume compared with 1.7% loss in Control Subjects ($p < 0.0001$).

Furthermore, the TLVR resulting from Zephyr EBV treatment was highly associated with improved FEV_1 in Zephyr EBV Subjects at 6 months of follow-up ($r^2 = 0.2785$, $p = 0.0000$).

Relevant clinical factors that would be associated with a closed system (exclusion of all lobar bronchi with Zephyr EBV devices and completeness of interlobar fissures to prevent collateral air flow) were highly associated with the degree of TLVR as measured by $TLAS_{TLC}$. Zephyr EBV Subjects with Technical Success (complete lobar exclusion) had a mean $TLAS_{TLC}$ of −28.1% compared with −11.1% for Zephyr EBV Subjects without Technical Success. Zephyr EBV Subjects with complete interlobar fissures had mean $TLAS_{TLC}$ of −40.1% (left lung) and −33.0% (right lung) compared with −20.7% and −4.4% respectively for incomplete fissures. The combination of Technical Success and Complete Fissure Integrity resulted in a mean $TLAS_{TLC}$ of −54.8% compared with −6.4% when both factors were absent.

Zephyr EBV treatment (Section 8.2), Technical Success (Section 10.3.1) and Fissure Integrity (Section 10.3.3) were also significantly associated with greater change in FEV_1 in Zephyr EBV Subjects when these factors were present.

13.0 SAFETY PROFILE AT ONE YEAR

13.1 Introduction

Adverse events were categorized and aggregated to allow characterization of the safety profile of Zephyr EBV Subjects compared with Control Subjects. In addition, several specific categories of adverse events specific to Zephyr EBV Subjects were analyzed. These safety evaluations are presented as follows:

13.2 Review of Adverse Events

13.2.1 Adverse Events

Adverse events through 1 year of follow-up are summarized in the following table.

Table 78 Adverse Events through 1 year

Adverse Events through 1 year	Control % (95% CI)	Zephyr EBV % (95% CI)	p value [1]
All-Cause Mortality [2]	3.5% (0.7 – 9.8%)	3.7% (1.6 – 7.2%)	1.0000
All Cardiovascular	6.9% (2.6 – 14.4%)	7.9% (4.7 – 12.4%)	1.0000
Arrhythmia	4.6% (1.3 – 11.4%)	6.1% (3.3 – 10.2%)	0.7856
CHF	1.2% (0.0 – 6.2%)	0.5% (0.0 – 2.6%)	0.4952
CAD	1.2% (0.0 – 6.2%)	1.9% (0.5 – 4.7%)	1.0000
Other Cardiac	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
Cerebrovascular Disease	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
TIA	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
Stroke	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Thromboembolic Disease	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Deep Vein Thrombosis	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Pulmonary Embolism	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
All COPD/Emphysema	62.1% (51.0 – 72.3%)	77.6% (71.4 – 83.0%)	**0.0095**
COPD Exacerbation	57.5% (46.4 – 68.0%)	72.4% (65.9 – 78.3%)	**0.0141**
COPD with hospitalization	10.3% (4.8 – 18.7%)	18.2% (13.3 – 24.1%)	0.1174
COPD w/o hospitalization	50.6% (39.6 – 61.5%)	57.5% (50.6 – 64.2%)	0.3069
Other Pulmonary Infection	1.2% (0.0 – 6.2%)	8.4% (5.1 – 13.0%)	**0.0174**
Increased SOB	2.3% (0.3 – 8.1%)	9.8% (6.2 – 14.6%)	**0.0295**
Cough	1.2% (0.0 – 6.2%)	6.1% (3.3 – 10.2%)	0.0748
Bronchospasm	0.0% (0.0 – 4.2%)	1.9% (0.5 – 4.7%)	0.3277
Any Respiratory Failure	3.5% (0.7 – 9.8%)	3.3% (1.3 – 6.6%)	1.0000
≥ 24 hours ventilation [2]	2.3% (0.3 – 8.1%)	2.8% (1.0 – 6.0%)	1.0000
< 24 hours ventilation	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
No ventilation	1.2% (0.0 – 6.2%)	0.5% (0.0 – 2.6%)	0.4952
Pneumonia Not Distal to Valve	10.3% (4.8 – 18.7%)	11.2% (7.3 – 16.2%)	1.0000
RV Increase from BL>15%	1.2% (0.0 – 6.2%)	0.5% (0.0 – 2.6%)	0.4952
Altered ABGs	1.2% (0.0 – 6.2%)	8.4% (5.1 – 13.0%)	**0.0174**
New/worse hypercapnia	1.2% (0.0 – 6.2%)	2.3% (0.8 – 5.4%)	0.6765
Hypoxemia	0.0% (0.0 – 4.2%)	7.0% (4.0 – 11.3%)	**0.0073**
All Pulmonary/Thoracic	9.2% (4.1 – 17.3%)	52.8% (45.9 – 59.7%)	**<0.0001**
Hemoptysis	2.3% (0.3 – 8.1%)	42.5% (35.8 – 49.5%)	**<0.0001**
Massive Hemoptysis [2]	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Other Hemoptysis	2.3% (0.3 – 8.1%)	42.1% (35.4 – 49.0%)	**<0.0001**
Pneumothorax	2.3% (0.3 – 8.1%)	5.1% (2.6 – 9.0%)	0.3602
Air leak > 7 days [2]	1.2% (0.0 – 6.2%)	1.9% (0.5 – 4.7%)	1.0000
Expanding Pneumothorax	2.3% (0.3 – 8.1%)	1.9% (0.5 – 4.7%)	1.0000
Stable Pneumothorax	1.2% (0.0 – 6.2%)	1.4% (0.3 – 4.0%)	1.0000
Empyema [2]	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
Pleural Effusion	0.0% (0.0 – 4.2%)	0.5% (0.0 – 2.6%)	1.0000
Other Pulmonary/Thoracic AEs	6.9% (2.6 – 14.4%)	21.0% (15.8 – 27.1%)	**0.0022**
Non–cardiac Chest Pain	3.5% (0.7 – 9.8%)	16.4% (11.7 – 22.0%)	**0.0018**
Lung Mass/Cancer	2.3% (0.3 – 8.1%)	0.9% (0.1 – 3.3%)	0.5820
ARDS	0.0% (0.0 – 4.2%)	0.0% (0.0 – 1.7%)	--
Fractured Rib	0.0% (0.0 – 4.2%)	0.9% (0.1 – 3.3%)	1.0000
Wheezing Non–valve Related	1.2% (0.0 – 6.2%)	4.7% (2.3 – 8.4%)	0.1865

Adverse Events through 1 year	Control % (95% CI)	Zephyr EBV % (95% CI)	p value [1]
All Valve / Implant Related		18.2% (13.3 – 24.1%)	
Expectoration/Aspiration/Migration		7.9% (4.7 – 12.4%)	
Pneumonia Distal to Valve [2]		4.2% (1.9 – 7.8%)	
Adverse tracheobronchial effect		8.4% (5.1 – 13.0%)	
Bronchial granulation tissue		7.9% (4.7 – 12.4%)	
Bronchial ulceration		0.0% (0.0 – 1.7%)	
Bronchial trauma		0.5% (0.0 – 2.6%)	
Dysphonia		1.4% (0.3 – 4.0%)	
All General AEs	33.3% (23.6 – 44.3%)	49.1% (42.2 – 56.0%)	**0.0150**
Non–pulmonary infections	18.4% (10.9 – 28.1%)	19.2% (14.1 – 25.1%)	1.0000
Upper respiratory infections	13.8% (7.3 – 22.9%)	15.4% (10.9 – 21.0%)	0.8588
Other non–pulmonary infections	5.8% (1.9 – 12.9%)	4.7% (2.3 – 8.4%)	0.7712
Fever	1.2% (0.0 – 6.2%)	3.3% (1.3 – 6.6%)	0.4458
Other Pain	4.6% (1.3 – 11.4%)	7.0% (4.0 – 11.3%)	0.6028
Gastrointestinal Adverse Events	4.6% (1.3 – 11.4%)	7.9% (4.7 – 12.4%)	0.4540
Nausea or Vomiting	1.2% (0.0 – 6.2%)	8.4% (5.1 – 13.0%)	**0.0174**
Other General	12.6% (6.5 – 21.5%)	22.9% (17.5 – 29.1%)	0.0554

[1] Two-sided Fisher's exact test
[2] A component of the Major Complications Composite (MCC) as defined in Section 4.5.5
Source: Attachment 3, Amended Statistical Analysis Report, Table 16:12

Over 1 year of follow-up, subjects in the two groups had equivalent all-cause mortality rates; 3.5% in Control Subjects and 3.7% in Zephyr EBV Subjects ($p = 1.0000$). Cardiovascular events were 6.9% in Control Subjects and 7.9% in Zephyr EBV Subjects ($p = 1.000$).

The VENT Pivotal Study revealed the high degree of pulmonary morbidity present in subjects with severe heterogeneous emphysema, with 77.6% of Zephyr EBV Subjects and 62.1% of Control Subjects having one or more COPD / emphysema category adverse events; this difference was significant ($p = 0.0095$). This difference was driven by the following subcategories of adverse events: COPD exacerbation (72.4% Zephyr EBV Subjects and 57.5% Control Subjects, $p = 0.0141$, Other Pulmonary Infection (8.4% compared with 1.2% respectively, $p = 0.0174$), Increased SOB (9.8% compared with 2.3% respectively, $p = 0.0295$) and Altered ABGs (8.4% compared with 1.2% respectively, $p = 0.0174$).

The rate of pulmonary / thoracic adverse events was higher in Zephyr EBV Subjects, 52.8%, compared with Control Subjects, 9.2% ($p < 0.0001$). This difference was driven by the following subcategories of adverse events: hemoptysis (42.1% Zephyr EBV Subjects compared with 2.3% in Control Subjects, $p < 0.0001$), and Noncardiac Chest Pain (16.4% compared with 3.5%, $p = 0.0018$).

Specific adverse events were associated with the Zephyr EBV. Granulation tissue narrowing the airways adjacent to the valves was observed in 7.9% (17 of 214) of implanted Zephyr EBV Subjects. Eight (8) of 214 Zephyr EBV Subjects (3.7%) expectorated one or more valves and 4.2% (9 of 214) of implanted Zephyr EBV Subjects experienced valve migrations without expectoration during study follow-up. Nine (9) Zephyr EBV Subjects (4.2%) had pneumonia distal to the valves during study follow-up.

General AEs occurred more frequently in Zephyr EBV Subjects (49.1%) compared with Control Subjects (33.3%, $p = 0.0150$); this appeared to be driven by procedure-related nausea or vomiting (8.4% vs. 1.2%, $p = 0.0174$) and a range of infrequent events (22.9% vs. 12.6%, $p = 0.0554$) including headache, sore throat, nose bleed, rhinitis, and lower leg / ankle edema. This may have been driven in part by detection bias in the more intently observed treatment group.

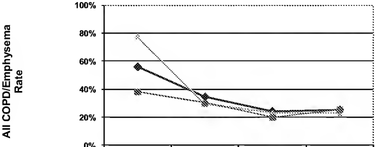
13.2.2 Adverse Events by Quarter

Events that were significantly higher at 1 year in Zephyr EBV Subjects than in Control Subjects included COPD Exacerbations, Other Pulmonary Infections, Increased Shortness of Breath, Hypoxemia, Hemoptysis, Non-cardiac Chest Pain, and General Adverse Events. The Figures below examine these events by quarter of follow-up in order to understand which events are short term and potentially triggered by the intervention and which are longer term and more likely due to the presence of the implant. This is further illustrated by separating Zephyr EBV Treatment event rates by those Subjects with one or more valves removed post-procedure and those Subjects with no valve removals post-procedure.

COPD Exacerbations adverse event rates were aggregated with other emphysema-related and pulmonary adverse events in All COPD/Emphysema Rates.

The All COPD/Emphysema rate declines in the Treatment with No Valve Removals group and the Treatment with Valve Removals group (see Figure 15) over the follow-up period. The overall decline in the All COPD/Emphysema rates appears to be independent of valve removals and the adverse event rate for the Treatment with No Valve Removals group approaches the adverse event rate for the Control group by the fourth quarter of follow-up.

Figure 15 Chart: All COPD/Emphysema Rates by Valve Removal by Quarter

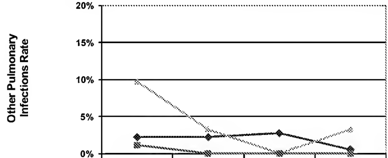


	Day 0 - 97	Day 98-194	Day 195 - 284	Day 284 - 386
Tx -No Removals, n=183	55.7%	34.4%	24.0%	25.1%
Tx -With Removals, n=31	77.4%	29.0%	22.6%	22.6%
Control, n=87	37.9%	29.9%	19.5%	25.3%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:4

The Other Pulmonary Infections rate declines in the Treatment with No Valve Removals group in the fourth quarter and the rate in the Treatment with Valve Removals group declines after the second quarter (see Figure 16). The rates are low for both groups and it is unclear whether the overall decline in the Other Pulmonary Infections rate is related to valve removals.

Figure 16 Chart: Other Pulmonary Infection Rates by Valve Removal by Quarter

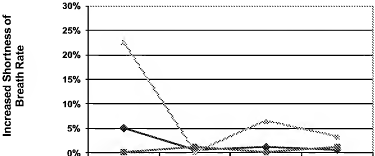


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	2.2%	2.2%	2.7%	0.6%
Tx - With Removals, n=31	9.7%	3.2%	0.0%	3.2%
Control, n=87	1.2%	0.0%	0.0%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:11

The occurrence of shortness of breath was nominally higher in the first 3 quarters for Zephyr EBV Subjects relative to Control Subjects, and then dropped in the fourth quarter. This decline in Shortness of Breath rates occurred in Zephyr EBV Subjects with valve removals as well as independent of valve removals.

Figure 17 Chart: Increased Shortness of Breath Rates by Valve Removal by Quarter

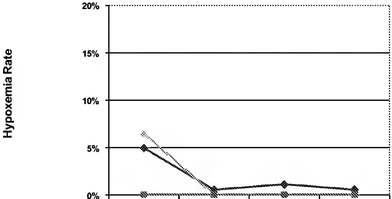


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	4.9%	0.6%	1.1%	0.6%
Tx - With Removals, n=31	22.6%	0.0%	6.5%	3.2%
Control, n=87	0.0%	1.2%	0.0%	1.2%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:5

Zephyr EBV Treatment Subjects and Control Subjects had similar rates of Hypoxemia after the first three months of the follow-up interval regardless if the Subject had valves removed or not.

Figure 18 Chart: Hypoxemia Rates by Valve Removal by Quarter

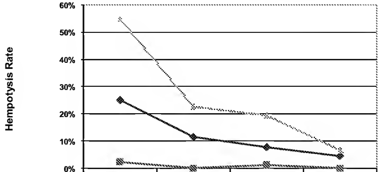


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n =183	4.9%	0.6%	1.1%	0.6%
Tx - With Removals, n=31	6.5%	0.0%	0.0%	0.0%
Control, n=87	0.0%	0.0%	0.0%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:8

Hemoptysis occurred at higher rates in Zephyr EBV Subjects, and although this did not fall to the same level as Control Subjects, it decreased substantially every quarter of study follow-up. This decline in Hemoptysis rates occurred in both the Treatment with Valve Removals and the Treatment with No Valve Removal groups.

Figure 19 Chart: Hemoptysis Rates by Valve Removal by Quarter

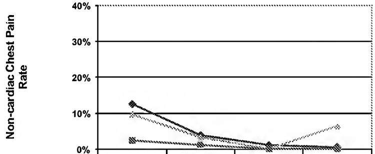


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	25.1%	11.5%	7.7%	4.4%
Tx - With Removals, n=31	54.8%	22.6%	19.4%	6.5%
Control, n=87	2.3%	0.0%	1.2%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:9

Non-cardiac Chest Pain was significantly higher in Zephyr EBV Subjects than in Control Subjects in the first quarter of follow up. These events appear to be transient and resolve independent of valve removal.

Figure 20 Chart: Non-cardiac Chest Pain Rates by Quarter

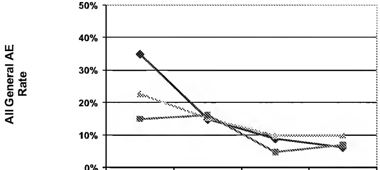


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	12.6%	3.8%	1.1%	0.6%
Tx - With Removals, n=31	9.7%	3.2%	0.0%	6.5%
Control, n=87	2.3%	1.2%	0.0%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:12

General Adverse Events, which included post-procedural Nausea or Vomiting, occurred at a higher rate in Zephyr EBV Treatment Subjects in the first quarter after randomization, but declined steadily throughout the study follow up period to rates similar to Control Subjects. These declines in the Treatment group appear to be independent of valve removals.

Figure 21 Chart: General Adverse Event Rates by Quarter



	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	35.0%	14.8%	8.7%	6.0%
Tx - With Removals, n=31	22.6%	15.1%	9.7%	9.7%
Control, n=87	14.9%	16.1%	4.6%	6.9%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:15

13.2.3 Serious Adverse Events

Serious adverse events (SAEs) through 1 year of follow-up are summarized in the following table.

Table 79 Per-Subject Serious Adverse Events through 1 Year

Serious Adverse Events through 1 year	Control n = 87 % (95% CI)	Zephyr EBV n = 214 % (95% CI)	p value [1]
All-Cause Mortality [2]	3.5% (0.7 - 9.8%)	3.7% (1.6 - 7.2%)	1.0000
All Cardiovascular	4.6% (1.3 - 11.4%)	4.2% (1.9 - 7.8%)	1.0000
Arrhythmia	2.3% (0.3 - 8.1%)	2.3% (0.8 - 5.4%)	1.0000
CHF	1.2% (0.0 - 6.2%)	0.5% (0.0 - 2.6%)	0.4952
CAD	1.2% (0.0 - 6.2%)	1.9% (0.5 - 4.7%)	1.0000
Other Cardiac	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Cerebrovascular Disease	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
TIA	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Stroke	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
Thromboembolic Disease	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Deep Vein Thrombosis	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Pulmonary Embolism	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--

Serious Adverse Events through 1 year	Control n = 87 % (95% CI)	Zephyr EBV n = 214 % (95% CI)	p value [1]
All COPD/Emphysema	18.4% (10.9 - 28.1%)	28.5% (22.6 - 35.1%)	0.0805
COPD Exacerbation	10.3% (4.8 - 18.7%)	23.4% (17.9 - 29.6%)	**0.0101**
COPD with hospitalization	10.3% (4.8 - 18.7%)	18.2% (13.3 - 24.1%)	0.1174
COPD w/o hospitalization	0.0% (0.0 - 4.2%)	2.8% (1.0 - 6.0%)	0.1867
Other Pulmonary Infection	0.0% (0. 0 - 4.2%)	3.3% (1.3 - 6.6%)	0.1989
Increased SOB	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Cough	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Bronchospasm	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Any Respiratory Failure	3.5% (0.7 - 9.8%)	3.3% (1.3 - 6.6%)	1.0000
≥ 24 hours ventilation [2]	2.3% (0.3 - 8.1%)	2.8% (1.0 - 6.0%)	1.0000
< 24 hours ventilation	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
No ventilation	1.2% (0.0 - 6.2%)	0.5% (0.0 - 2.6%)	0.4952
Pneumonia Not Distal to Valve	9.2% (4.1 - 17.3%)	7.0% (4.0 - 11.3%)	0.4847
RV Increase from BL>15%	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Altered ABGs	0.0% (0.0 - 4.2%)	2.8% (1.0 - 6.0%)	0.1867
New/worse hypercapnia	0.0% (0.0 - 4.2%)	1.4% (0.3 - 4.0%)	0.5594
Hypoxemia	0.0% (0.0 - 4.2%)	1.9% (0.5 - 4.7%)	0.3277
All Pulmonary/Thoracic	3.5% (0.7 - 9.8%)	17.3% (12.5 - 23.0%)	**0.0007**
Hemoptysis	0.0% (0.0 - 4.2%)	12.2% (8.1 - 17.3%)	**<0.0001**
Massive Hemoptysis [2]	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
Other Hemoptysis	0.0% (0.0 - 4.2%)	11.7% (7.7 - 16.8%)	**0.0003**
Pneumothorax	2.3% (0.3 - 8.1%)	4.7% (2.3 - 8.4%)	0.5192
Air leak > 7 days [2]	1.2% (0.0 - 6.2%)	1.9% (0.5 - 4.7%)	1.0000
Expanding Pneumothorax	2.3% (0.3 - 8.1%)	1.9% (0.5 - 4.7%)	1.0000
Stable Pneumothorax	0.0% (0.0 - 4.2%)	0.9% (0.1 - 3.3%)	1.0000
Empyema [2]	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Pleural Effusion	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Other Pulmonary/Thoracic AEs	1.2% (0.0 - 6.2%)	1.4% (0.3 - 4.0%)	1.0000
Non-cardiac Chest Pain	0.0% (0.0 - 4.2%)	0.9% (0.1 - 3.3%)	1.0000
Lung Mass/Cancer	1.2% (0.0 - 6.2%)	0.0% (0.0 - 1.7%)	0.2890
ARDS	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Fractured Rib	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
Wheezing Non-valve Related	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
All Valve / Implant Related		15.9% (11.3 - 21.5%)	
Expectoration/Aspiration/Migration		7.5% (4.3 - 11.9%)	
Pneumonia Distal to Valve [2]		4.2% (1.9 - 7.8%)	
Adverse tracheobronchial effect		7.0% (4.0 - 11.3%)	
Bronchial granulation tissue		6.5% (3.6 - 10.7%)	
Bronchial ulceration		0.0% (0.0 - 1.7%)	
Bronchial trauma		0.5% (0.0 - 2.6%)	
Dysphonia		0.0% (0.0 - 1.7%)	

Serious Adverse Events through 1 year	Control n = 87 % (95% CI)	Zephyr EBV n = 214 % (95% CI)	p value [1]
All General AEs	5.8% (1.9 - 12.9%)	8.9% (5.4 - 13.5%)	0.4833
Non-pulmonary infections	1.2% (0.0 - 6.2%)	1.4% (0.3 - 4.0%)	1.0000
Upper respiratory infections	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Other non-pulm. infections	1.2% (0.0 - 6.2%)	1.4% (0.3 - 4.0%)	1.0000
Fever	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Other Pain	0.0% (0.0 - 4.2%)	0.5% (0.0 - 2.6%)	1.0000
Gastrointestinal Adverse Events	1.2% (0.0 - 6.2%)	3.7% (1.6 - 7.2%)	0.4551
Nausea or Vomiting	0.0% (0.0 - 4.2%)	0.0% (0.0 - 1.7%)	--
Other General	3.5% (0.7 - 9.8%)	5.1% (2.6 - 9.0%)	0.7640

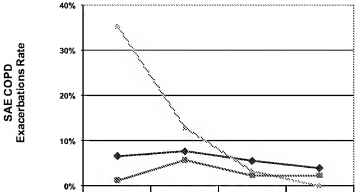
[1] Two-sided Fisher's exact test
[2] A component of the Major Complications Composite (MCC) as defined in Section 4.5.5
Source: Attachment 3, Amended Statistical Analysis Report, Figure 16:19

The significant differences between treatment groups included COPD / Emphysema SAEs, which were higher in Zephyr EBV Subjects (23.4%) compared with Control Subjects (10.3%, p = 0.0101); driven predominantly by those exacerbations requiring hospitalization. The occurrence of Pulmonary / Thoracic SAEs was higher in Zephyr EBV Subjects (17.3%) compared with Control Subjects (3.5%, p = 0.0007); this was driven by the rate of hemoptysis (12.2% vs. 0.0%, p < 0.0001). The remaining rates of SAEs were not significantly different between the Zephyr EBV Subjects and Control Subjects.

13.2.4 Serious Adverse Events by Quarter

The disproportion of SAEs occurring in relation to use of the Zephyr EBV was more pronounced during the first 3 to 6 months after valve placement, following the trend of the adverse events overall. SAE COPD Exacerbation rates for Zephyr EBV Subjects approached the rates for Control Subjects in the fourth quarter of study follow-up. SAE COPD Exacerbations in the first quarter were often treated with valve removal. Zephyr EBV Treatment Subjects experienced SAE COPD Exacerbations at a declining rate after the first six months of follow-up independent of valve removal.

Figure 22 Chart: SAEs – COPD Exacerbations Rates by Valve Removal by Quarter

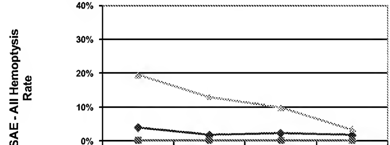


	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No Removals, n=183	6.6%	7.7%	5.5%	3.8%
Tx - With Removals, n=31	35.5%	12.9%	3.2%	0.0%
Control, n=87	1.2%	5.8%	2.3%	2.3%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:13

The rate of Zephyr EBV Treatment Subjects with SAE Hemoptysis declined over the 1-year study follow-up period.

Figure 23 Chart: SAEs – All Hemoptysis Rates by Quarter



	Day 0 - 97	Day 98 - 194	Day 195 - 284	Day 285 - 386
Tx - No removals, n=183	3.8%	1.6%	2.2%	1.6%
Tx - With removals, n=31	19.4%	12.9%	9.7%	3.2%
Control , n=87	0.0%	0.0%	0.0%	0.0%

Source: Attachment 3, Amended Statistical Analysis Report, Figure 19:14

13.2.5 Device-Related Adverse Events

All adverse events were adjudicated by the CEC, which categorized each event as Not Related, Remote, Possible, or Probable with respect to the Zephyr EBV Device-relatedness or Procedural relatedness. The tables below summarize the CEC findings for events during the procedure hospitalization and for events occurring after discharge for the procedure.

Of the 118 adverse events reported in Zephyr EBV Subjects <u>during</u> the initial procedure hospitalization, 40.7% were not related, 5.9% were remote, 40.7% were possible, and 12.7% were probable with respect to <u>device-relatedness</u>. The 15 "probable" device-related adverse events during the initial hospitalization included hypoxemia (2), prolonged air leak (2), stable pneumothorax (2), pleural effusion (1), non-cardiac chest pain (6), wheezing not related to the valve (1) and pneumonia distal to valve (1).

Please refer to Attachment 3, Amended Statistical Analysis Report, Table 18:1 for detailed tabulation.

Of the 734 adverse events reported in Zephyr EBV Subjects <u>after</u> the initial procedure hospitalization, 28.5% were not related, 36.0% were remote, 27.7% were possible, and 7.9% were probable with respect to <u>device-relatedness</u>. The 58 "probable" device-related adverse events after the initial hospitalization included death (1), hypoxemia (1), massive hemoptysis (1), other hemoptysis (18), expanding pneumothorax (2), wheezing not related to the valve (7), pneumonia distal to valve (8) and bronchial granulation tissue (20).

Please refer to Attachment 3, Amended Statistical Analysis Report, Table 18:2 for detailed tabulation.

13.2.6 Procedure-Related Adverse Events

Of the 118 adverse events reported in Zephyr EBV Subjects <u>during</u> the initial procedure hospitalization, 12.7% were not related, none were remote, 2.5% were possible, and 84.7% were probable with respect to <u>procedure-relatedness</u>. The 100 "probable" procedure-related adverse events during the initial hospitalization included general cardiovascular (1), arrhythmia (1), COPD exacerbation with hospitalization (1), COPD exacerbation without hospitalization (2), increased SOB (4), cough (4), bronchospasm (3), new or worsening hypercapnia (4), hypoxemia (8), hemoptysis (22), prolonged pneumothorax (2), expanding pneumothorax (1), stable pneumothorax (3), pleural effusion (1), non-cardiac chest pain (12), valve expectoration (2), bronchial trauma (1), dysphonia (3), and other general adverse events (26).

Please refer to Appendix 7-5-8, Statistical Analysis of the VENT Pivotal Trial, Table 18:5 for detailed tabulation.

Of the 734 adverse events reported in Zephyr EBV Subjects after the initial procedure hospitalization, 78.7% were not related, 8.4% were remote, 8.3% were possible, and 4.5% were probable with respect to procedure-relatedness. The 33 "probable" procedure-related adverse events after the initial hospitalization included COPD exacerbation with hospitalization (1), COPD exacerbation without hospitalization (1), increased SOB (2), cough (4), bronchospasm (1), hypoxemia (1), other hemoptysis (10), wheezing not related to valve (1), valve expectoration/migration (3) and other general adverse events (9).

Please refer to Attachment 3, Amended Statistical Analysis Report, Table 18:6 for detailed tabulation.

13.3 Zephyr EBV Subjects with Specific Adverse Events

13.3.1 Granulation Tissue

During symptom-driven bronchoscopy, 17 Zephyr EBV Subjects (7.9% of 214 subjects) were found to have granulation tissue narrowing the airways adjacent to valves during the course of study follow-up. These subjects developed moderate tissue formation adjacent to one or more valves. The observed granulation tissue was felt to be typical reactive tissue that can form adjacent to any foreign body present in the airways, such as that which forms at the distal end of an indwelling metal tracheostomy.

Table 80 Zephyr EBV Subjects with Granulation Tissue

Subject ID	Action Taken	Days Post-Procedure
	Valve Removal	86[1]
	Electrocautery & Topical Mitomycin Electrocautery & Topical Mitomycin Electrocautery & Topical Mitomycin	124 231 351
	Valve Removal	166
	Valve Removal	194
	Valve Removal	25
	Valve Removal	327
	Exploratory Bronchoscopy	198
	None	146
	Drug Therapy	34
	Valve Removal	275
	Valve Removal	19

	Action Taken	Days Post-Procedure
	Valve Removal	288
	Valve Removal	244
	Valve Removal	211
	Valve Removal	88
	Valve Removal	84
	Exploratory Bronchoscopy Cryotherapy	83 113

ranulation tissue was diagnosed during Valve Removal procedure. Valve Removal ot a result of diagnosis of Granulation Tissue.
Source: P070025, September 21, 2007, Volume 011, Page 122

13.3.2 Valve Expectoration or Migration*

Valve migration occurred when the valve was not retained in the original position within the target bronchus. Valve migration outside the target bronchus occurred when the valve migrated to a non-target bronchus, and valve expectoration occurred when the valve migrated out of the target bronchus and was subsequently coughed out by the subject. Seventeen (17) Zephyr EBV Subjects (7.9% of 214) experienced valve migration. Of these, 9 subjects (4.2%) had 1 or more valves that migrated, but were not expectorated, 6 subjects (2.8%) expectorated 1 or more valves, and 2 subjects (0.9%) had at least one migration without expectoration and at least one expectoration during the course of study follow-up.

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* Effort was made to obtain bronchoscopic video of the placement procedure when valve migration was reported. Of the 23 instances of Zephyr EBV migration, procedural video was obtained for 14. A qualitative assessment was made by Emphasys technical personnel. They identified 3 probable root-causes for the migration (see bullet points below). Based on these findings, additional training was initiated. Additionally, a visual "marker band" (original PMA Vol. 001, Page 80) has been added to the distal end of the delivery catheter in order to aid physicians in calibrating the depth of the bronchial target and the longitudinal position of the valve relative to the carina of the target bronchus. This marker band was not implemented during the conduct of the study.

- Bronchial target too short for Zephyr EBV placement (2/14)
- Zephyr EBV placed too proximal within target bronchus (6/14)
- Bronchial target too large in diameter for Zephyr EBV placement (5/14)
- Zephyr EBV did not migrate – compared follow-up video to procedural video (1/14)

Table 81 Zephyr EBV Subjects with Valve Migrations or Expectorations

Zephyr EBV Group	% (n)
Subjects with Valve Migrations or Expectorations	7.9% (17 / 214)
Migration Only	4.2% (9 / 214)
One valve migrated within target bronchus	1.4% (3 / 214)
One valve migrated outside target bronchus	2.3% (5 / 214)
One valve migrated within, and 3 valves migrated outside target bronchus	0.5% (1 / 214)
Expectorated	3.7% (8 / 214)
One valve expectorated	2.3% (5 / 214)
Two valve expectorated	0.5% (1 / 214)
One valve expectorated and one valve migrated within target bronchus	0.5% (1 / 214)
One valve expectorated and one valve migrated outside target bronchus	0.5% (1 / 214)

Source: P070025, September 21, 2007, Volume 011, Page 123

There were 820 valves implanted and not removed procedurally in the 214 subjects with one or more valves implanted. Of these 820 valves, 23 valves (2.8%) in 17 subjects migrated or were expectorated. Of these, 4 valves (0.5%) migrated within the target bronchus, 10 migrated outside the target bronchus (1.2%), and 9 valves (1.1%) were expectorated. Fourteen (14) of these 17 Zephyr EBV Subjects had at least 1 migrated or expectorated valve replaced.

Table 82 Summary: Zephyr EBV Subjects with Valve Expectoration or Migration

Subject ID	Expectoration/Migration Description	Number of Valves	Action Taken	Days Post Procedure
	Contralateral migration	1	Valve removed - not replaced	274
	Expectoration from lungs	1	Valve replaced	20
	Migration within target bronchus	1	Valve removed - not replaced	244
	Expectoration from lungs	1	Valve replaced	3
	Contralateral migration	1	Valve removed and replaced	19
	Expectoration from lungs	1	Valve replaced	0
	Ipsilateral migration	1	Valve removed and replaced	66
	Contralateral migration	1	Valve removed and replaced	186
	Migration within target lobe	1	Valve removed and replaced	192
	Proximal Migration within target bronchus	1	Valve removed and replaced	224
	Contralateral migration	1	Valve removed and replaced	25
	Ipsilateral migration	1	Valve removed and replaced	38

Subject ID	Expectoration/Migration Description	Number of Valves	Action Taken	Days Post Procedure
	Expectoration from lungs	1	Valve not replaced	200
	Expectoration from lungs	1	Valve replaced	0
	Expectoration from lungs	1	Valve not replaced	16
	Distal Migration within target bronchus	1	Valve left in place - additional valve placed adjacent to existing valve	100
	Expectoration from lungs	1	Valve replaced	2
	Proximal Migration within target bronchus	1	Valve removed and replaced	12
	Ipsilateral migration	1	Valve removed and replaced	160
	Expectoration from lungs	1	Valve replaced	273
	Expectoration from lungs	1	Valve replaced	21
	Ipsilateral migration	1	All implanted valves removed - not replaced	0
	Proximal Migration within target bronchus	1	Valve removed and replaced	0
Total		**23**		

Source: P070025, September 21, 2007, Volume 011, Page 123-124.

13.3.3 Pneumonia Distal to Valves

Nine (9) Zephyr EBV Subjects (4.2%) had pneumonia distal to valves during the 1 year follow-up period. All subjects received drug therapy and valves were removed from 3 of the 9 subjects (33.3%). Eight (8) of the 9 resolved during the study follow-up period and one was ongoing at the end of the 1-year study follow-up period. The subject with an unresolved pneumonia distal to valves at study exit had been admitted for treatment (drug therapy and bronchoscopy) during the trial and was discharged on oral antibiotics three days post study exit. The valves in this subject were not removed during bronchoscopy.

Table 83 Zephyr EBV Subjects with Pneumonia Distal to Valves

	Actions Taken	Days Post Procedure	Resolved
[redacted]	Drug Therapy, Valve Removal	0[1]	Yes
	Drug Therapy, Bronchoscopy	356	Ongoing
	Drug Therapy, Hospitalization	163	Yes
	Drug Therapy	275	Yes
	Drug Therapy, Bronchoscopy, Hospitalization	230	Yes
	Drug Therapy	208	Yes
	Drug Therapy, Valve Removal	258	Yes
	Drug Therapy, Valve Removal	208	Yes
	Drug Therapy, Hospitalization	15	Yes

[1] Date of onset was reported by site as Unknown. Earliest possible onset date was the date of the EBV procedure.
Source: P070025, September 21, 2007, Volume 011, Page 125

13.3.4 Massive Hemoptysis

Subject [redacted] complained of recurrent hemoptysis, possible vomiting of blood, and dyspnea between the original procedure and Day 8 of follow-up. On Day 8, the subject experienced increased hemoptysis followed by cardiorespiratory arrest. He was intubated and ventilated, but after two weeks clear evidence of irreversible hypoxic brain led to withdrawal of support and subsequent death. Autopsy revealed advanced bullous emphysema with all 4 stents in position without perforation, migration or intrusion into blood vessels, and without any clear source of bleeding. This event was reviewed by the DSMB and promptly communicated to the FDA, IRBs and participating Investigators with recommendations for close monitoring of subjects with recurrent hemoptysis. No other case of massive hemoptysis occurred during study follow-up.

13.3.5 Valve Treatment for Persistent Air Leak

Subject [redacted] was a Zephyr EBV Subject who developed a complete left pneumothorax on the day after valve implantation. A chest tube was inserted and the pneumothorax significantly cleared. However, he continued to have a large, persistent air leak and subcutaneous emphysema. A Compassionate Use request to the FDA to utilize Zephyr EBVs to resolve this air leak was approved (G020230 / S39) and on the 9th day after implantation 2 additional Zephyr EBVs were placed in the superior segment of the left lower lobe after isolating the air leak by balloon occlusion. After the procedure, the air leak was significantly reduced, but a small air leak still remained. The chest tube was left in place after the procedure. The suction used on the chest tube was reduced after the procedure and the subject's air leak completely sealed eight days post Zephyr EBV Treatment. The chest tube was removed three days later and the subject was discharged

from the hospital the following day. The subject was evaluated 2 – 3 weeks from discharge and was reported as returning to normal activities.

13.4 Valve Removal during Study Follow-Up

Thirty-one (31, 14.5%) of Zephyr EBV Subjects underwent the removal of one or more Zephyr EBV valves during the course of study follow-up. Eighty seven (87) valves underwent one or more remova[redacted]h 85 of the 87 valves (97.7%) being successfully removed. Subject [redacted] had a total of 4 valves removed in 4 separate procedures: 2 valves successfully removed in two procedures, followed by a third procedure in which 2 additional valves could not be removed, followed two days later by removal of those 2 valves. Subject [redacted] had 4 of 5 valves removed successfully in a first procedure and the 5th valve successfully removed 50 days later. The only 2 valves which were not successfully retrieved were in Subjec[redacted] who had 2 of 4 attempted valves removed in a single procedure and no subsequent procedure to attempt removal of the remaining 2 valves.

Table 84 Per-Subject Reasons for Attempted Valve Removal during Study Follow-up

Zephyr EBV Group (per subject)	% (n) [1]
Migration	25.8% (8 / 31)
Post Obstructive Pneumonia	3.2% (1 / 31)
Pneumonia, Hemoptysis	3.2% (1 / 31)
Hemoptysis	3.2% (1 / 31)
Hemoptysis & Granulation Tissue	3.2% (1 / 31)
Granulation	3.2% (1 / 31)
Granulation and Migration	3.2% (1 / 31)
Subject's Request	22.6% (7 / 31)
Placed in Incorrect Airway	9.7% (3 / 31)
Increased Dyspnea	3.2% (1 / 31)
Continuing COPD Exacerbation	6.5% (2 / 31)
To Access Distal Airway for Biopsy	3.2% (1 / 31)
Other	9.7% (3 / 31)

[1] Denominator = 31 subjects with valve removal attempted
Source: P070025, September 21, 2007, Volume 011, Page 126

Twelve (12) valves were removed due to migration, 3 due to post-obstructive pneumonia, 5 due to hemoptysis, 8 due to granulation, 28 at the subject's request, 7 placed in incorrect airways, 3 due to increased dyspnea, and 7 due to continuing COPD exacerbations. Other reasons for valve removal included removal prior to LVRS, endobronchial erosion with suppuration, and to allow distal biopsy.

Of the 44 specific instances of valve removal, 33 resulted in resolution of the reason for that intervention in 25 of these 31 Zephyr EBV Subjects (80.6% resolution rate). The

unresolved adverse events in the 6 subjects without resolution despite valve removal were COPD exacerbation (1), pneumonia and hemoptysis (1), granulation tissue (1), hemoptysis (1), hemoptysis and granulation tissue (1) and endobronchial erosion and suppuration (1).

Table 85 Summary: Valve Removal during Study Follow-Up

Day [1]	Removal S / A [2]	Reason(s) for Removal	Status / Day [3]
160	1 / 1	Valve Migrated	Resolved / 160
70	4 / 4	Subject Request (Not feeling better)	Resolved / 71
134	5 / 5	Continuing COPD Exacerbation	Ongoing at study exit [4]
242	7 / 7	Subject Request (Worsened breathing)	Resolved / 243
296	1 / 1	Post-obstructive Pneumonia	Resolved / 301
132	4 / 4	Subject Request (Shortness of breath)	Resolved / 132
86 113 239 241	1 / 1 1 / 1 0 / 2 2 / *	Non-functioning Valve B2b Removed B2a to Place Large Valve in B2 Pneumonia and Continued Hemoptysis Pneumonia and Continued Hemoptysis	Resolved / 86 Resolved /113 Pneumonia: Resolved / 268; Hemoptysis: Ongoing at study exit; Pneumonia: Resolved / 268; Hemoptysis: Ongoing at study exit
38	2 / 2	Planned Removal [5]	Resolved / 38
166 263	1 / 1 3 / 3	Granulation Tissue Granulation Tissue	Ongoing at study exit Ongoing at study exit
111 188 194 224	1 / 1 1 / 1 1 / 1 1 / 1	Valve Migration Valve Migration Valve Migration Valve Migration	Resolved / 111 Resolved / 188 Resolved / 194 Resolved / 224
25 84	1 / 1 3 / 3	Valve Migration Granulation Tissue	Resolved / 25 Resolved / 84
29	1 / 1	Valve Migration	Resolved / 29
7	2 / 2	Placed in Incorrect Lobe	Resolved / 7
327 377	4 / 5 1 / *	Hemoptysis Hemoptysis	Ongoing at study exit [6] Ongoing at study exit [6]
25	3 / 3	Increased Dyspnea	Resolved / 39
85	4 / 4	Subject Request (No details)	Resolved / 85
78	1 / 1	Hemoptysis Granulation Tissue	Hemoptysis: Ongoing at study exit; Granulation Tissue: Ongoing at study exit
275	1 / 1	Valve Migration	Resolved / 275
294	3 / 3	Pre-LVRS	Resolved / 294
74	1 / 1	Valve Migration	Resolved / 74
25	1 / 1	Valve Migration	Resolved / 25
288	2 / 4	Subject Request (No details)	Resolved / 288
244	1 / 1	Valve Migration	Resolved / 244
120	3 / 3	Subject Request, Worsened PFTs (Not feeling better and worsened PFTs)	Resolved / 120

Subject ID	Day [1]	Removal S / A [2]	Reason(s) for Removal	Status / Day [3]
	19	2 / 2	Continuing COPD Exacerbation	Resolved / 29
	1	5 / 5	Placed in Incorrect Lobe	Resolved / 1
	211	4 / 4	Subject Request (No details)	Resolved / 211
	88	1 / 1	Valve Migration	Resolved / 88
	38	1 / 1	Valve Migration	Resolved / 38
	99	3 / 3	To Biopsy Mass Distal to Valves	Resolved / 99
	210	1 / 1	Endobronchial Erosion and Suppuration	Ongoing at study exit

[1] Day of removal procedure(s), based on Start Date(s) reported on Event Log
[2] S / A = successful / attempted removals
[3] Status / Day = Post-EBV Removal, status and resolution day of event that triggered valve removal attempt(s). Event was noted as "Resolved" if Stop Date was provided and "Ongoing" if Stop Date was not provided. If EBV removal was per subject's request, then status and resolution day of EBV Removal was reported.
[4] Subject prematurely discontinued study at Day 284 post-randomization.
[5] Tempo or air leak (compassionate use in Zephyr EBV study subject)
[6] Subject prematurely exited study; last visit was made on Day 183 post-randomization.
* Same valve(s) reattempted
Source: P070025, September 21, 2007, Volume 011, Page 127-128

13.5 Summary: Adverse Event Profile through One Year

Mortality: all-cause mortality was similar in the two groups through one year of follow-up, with 3.5% (95% CI 0.7 – 9.8%) of Control Subjects and 3.7% (95% CI 1.6 – 7.2%) of Zephyr EBV Subjects dying of any cause during the year. This difference was not significant.

COPD / Emphysema Adverse Events: The VENT Pivotal Study revealed the high degree of pulmonary morbidity present in subjects with severe heterogeneous emphysema, with 77.6% of Zephyr EBV Subjects and 62.1% of Control Subjects having one or more COPD / emphysema category adverse events; this difference was significant ($p = 0.0095$). This difference was driven by the following subcategories of adverse events: COPD exacerbation (72.4% Zephyr EBV Subjects and 57.5% Control Subjects, $p = 0.0141$, Other Pulmonary Infection (8.4% compared with 1.2% respectively, $p = 0.0174$), Increased SOB (9.8% compared with 2.3% respectively, $p = 0.0295$) and Altered ABGs (8.4% compared with 1.2% respectively, $p = 0.0174$).

When serious adverse events are examined only COPD Exacerbation is significantly different, with an 23.4% rate for Zephyr EBV Subjects and a 10.3% rate for Control Subjects ($p = 0.0101$).

Pulmonary / Thoracic Adverse Events: The rate of these adverse events was much higher in Zephyr EBV Subjects, 52.8%, compared with Control Subjects, 9.2% ($p < 0.0001$). This difference was driven by the following subcategories of adverse events:

hemoptysis (42.1% Zephyr EBV Subjects compared with 2.3% in Control Subjects, $p < 0.0001$), and Noncardiac Chest Pain (16.4% compared with 3.5%, $p = 0.0018$).

When serious adverse events are examined, only other hemoptysis remains significantly more frequent in Zephyr EBV Subjects, 11.7%, compared with 0.0% in Control Subjects ($p = 0.0003$).

General / Other Adverse Events: The remaining categories of adverse events occurred somewhat more frequently in Zephyr EBV Subjects, 49.1%, compared with Control Subjects, 33.3% ($p = 0.015$). Rates that were higher in Zephyr EBV Subjects included nausea and vomiting (often related to procedure sedation), headaches, sore throat and similar minor complaints.

There are no significant differences in the rate of serious adverse events for General / Other adverse events.

Resolution of Adverse Events: Most of these adverse event and serious adverse event rates decline after the first three months of follow-up, suggesting that the passage of time and when indicated removal of one or more valves are effective responses to these events.

Valve Expectoration or Migration: Of 820 implanted valves at the completion of the initial procedure, 23 (2.8%) migrated or were expectorated in 17 subjects between Days 0 and 274 without significant sequelae, and 14 subjects had at least one of these valves replaced during study follow-up.

Pneumonia Distal to Valves: 9 Zephyr EBV Subjects (4.2%) had pneumonia distal to valves and received drug therapy (9) and valve removal (3). Eight (8) of the 9 resolved during the study follow-up period and one subject, with onset on Day 356, was still under treatment at the end of the 1-year study follow-up period.

Massive Hemoptysis: One Zephyr EBV Subject experienced dyspnea and, hemoptysis between Days 0 and 8, and then presented in cardiorespiratory arrest on Day 8 and died thereafter of hypoxic brain damage. Autopsy revealed bullous emphysema, 4 intact and well-positioned valves, and no obvious source of bleeding.

Valve Treatment for Persistent Air Leak: One Zephyr EBV Subject developed complete left pneumothorax on Day 1, with only partial resolution after chest tube placement. Compassionate Use treatment with 2 additional valves in the superior segment of the left lower lobe significantly reduced but did not eliminate the air leak until 8 days later.

Valve Removal During Study Follow-Up: Thirty one (31, 14.5%) Zephyr EBV Subjects had one or more valves removed after the initial procedure. Eighty five (85) of 87 valves attempted were successfully removed (97.7%). Of these 31 subjects, 25 (80.6%) had resolution of the reason for the intervention following valve removal.

14.0 OUTCOME MEASURES AT ONE YEAR

14.1 Introduction

Although the VENT Pivotal Study was not designed to assess effectiveness outcomes past 6 months, *post hoc* assessments of effectiveness outcome measures were made for Completed Cases subjects with one year follow-up data. These analyses included:

- 14.2. Effectiveness Outcome Measures at 1 Year
  - 14.2.1. Percent Change in FEV_1 at 1 Year
  - 14.2.2. High Heterogeneity Percent Change in FEV_1 at 1 Year
  - 14.2.3. Percent Change in 6MWT at 1 Year
  - 14.2.4. High Heterogeneity Percent Change in 6MWT at 1 Year
  - 14.2.5. Change in SGRQ at 1 Year
  - 14.2.6. Change in mMRC Dyspnea Scale at 1 Year
  - 14.2.7. Change in Maximum Workload during Cycle Ergometry at 1 Year
  - 14.2.8. Change in Use of Supplemental Oxygen at 1 Year
- 14.3. Matched 6 Month and 1 Year FEV1 and 6MWT Data
  - 14.3.1. Matched 6 Month and 1 Year FEV_1 Outcomes
  - 14.3.2. High Heterogeneity Matched 3, 6, and 12 Month FEV_1 Outcomes
  - 14.3.3. Matched 6-Month and 1-Year 6MWT Outcomes
  - 14.3.4. High Heterogeneity Matched 3, 6, and 12 Month 6MWT Outcomes
- 14.4. Summary: Effectiveness Outcome Measures at 1 Year

14.2 Effectiveness Outcome Measures at 1 Year

14.2.1 Percent Change in FEV_1 at 1 Year

At the end of 1 year of follow-up, Completed-Cases Zephyr EBV Subjects demonstrated a 6.7% higher FEV_1 and Control Subjects a 1.4% lower FEV_1, for an 8.1% net difference between the two groups (95% CI 4.0, 12.2%). This persistent Zephyr EBV treatment benefit was slightly larger than the 7.2% net difference observed at 6 months.

Table 86 Percent Change in FEV_1 at 1 Year (CC)

FEV_1 – % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	–1.4 (10.8) 74 –1.7 (–29.1, 31.6)	6.7 (22.1) 175 2.0 (–34.2, 88.4)	8.1 (4.0, 12.2)

[1] Difference in means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 15:1

14.2.2 High Heterogeneity Subgroup: Percent Change in FEV_1 at 1 Year

In the High Heterogeneity Subgroup at the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a 13.6% higher FEV_1 and Control Subjects a 1.6% lower FEV_1, for a 15.2% net difference between the two groups (95% CI 9.1, 21.2%). This persistent Zephyr EBV treatment benefit was greater than the 8.1% net difference observed in the entire CC cohort at 1 year.

Table 87 High Heterogeneity Subgroup: Percent Change in FEV_1 at 1 Year (CC)

FEV_1 – % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	-1.6 (10.4) 41 0.0 (-29.1, 21.8)	13.6 (24.2) 87 10.2 (-32.5, 88.4)	15.2 (9.1, 21.2)

[1] Difference in means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:11

14.2.3 Percent Change in 6MWT at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of 6MWT demonstrated a 0.4% reduction and Control Subjects a 3.9% reduction, for a 3.7% net Zephyr EBV treatment benefit (95% CI 1.8, 9.2%).

Table 88 Percent Change in 6MWT at 1 Year (CC)

6MWT – % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	–3.9 (16.9) 75 -3.2 (-63.1, 31.6)	–0.4 (26.3) 173 1.1(-98.3, 108.0)	3.6 (–1.8, 9.2)

[1] Difference in means and unequal variance t-test confidence interval (-3.9)- (-0.4) = 3.6 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 15:2

14.2.4 High Heterogeneity Subgroup: Percent Change in 6MWT at 1 Year

In the High Heterogeneity Subgroup at the end of 1 year of follow-up, Zephyr EBV Subjects demonstrated a 3.1% higher 6MWT and Control Subjects a 5.0% reduction, for an 8.2% net Zephyr EBV treatment benefit (95% CI −0.4, 16.7%).

Table 89 High Heterogeneity Subgroup: Percent Change in 6MWT at 1 Year (CC)

FEV_1 – % Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)[1]
CC Subjects	-5.0 (19.2) 41 -3.5 (-63.1, 29.5)	3.1 (29.2) 87 3.2 (-75.6, 108.0)	8.2 (-0.4, 16.7)

[1] Difference in means and unequal variance t-test confidence interval (3.1)- (-5.0) = 8.2 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:11

14.2.5 Change in SGRQ at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of SGRQ demonstrated a mean 1.7 point improvement (score reduction) and the Control Subjects had a mean 1.2 point deterioration (score increase), a net Zephyr EBV treatment benefit of −2.8 (95% CI −6.2, 0.6).

Table 90 Change in SGRQ at 1 Year (CC)

SGRQ – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	1.3 (9.0) 61 0.9 (-19.7, 28.7)	-1.7 (14.4) 149 -2.1 (-39.3, 46.6)	-3.0 (-6.3, 0.2) [1]

[1] Difference in means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1

14.2.6 Change in mMRC Dyspnea Scale at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of the mMRC Dyspnea Scale demonstrated a mean 0.03 point deterioration (score increase) and the Control Subjects had a mean 0.14 point deterioration (score increase), no difference of –0.0 (95% CI –0.0, 0.0).

Table 91 Change in mMRC Dyspnea Scale at 1 Year

mMRC – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta[1] (95% CI)[2]
Subjects	0.14 (1.09) 66 0.00 (-3.00, 4.00)	0.03 (1.10) 159 0.00 (-4.00, 3.00)	0.00 [3] (0.00, 0.00) [4]

[1] Difference in medians
[2] Non-parametric confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1

14.2.7 Change in Maximum Workload during Cycle Ergometry at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of maximum workload during cycle ergometry had a mean 2.0 watt deterioration and the Control Subjects had a mean 5.1 watt deterioration, a net Zephyr EBV treatment benefit of 3.2 watts (95% CI −0.8, 7.2).

Table 92 Change in Maximum Workload during Cycle Ergometry at 1 Year (CC)

Cycle Ergometry – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects	-5.1 (12.3) 69 0.0 (-50.0, 20.0)	-2.0 (17.3) 154 0.00 (-120.0, 50.0)	3.2 (-0.8, 7.2) [1]

[1] Difference of means and unequal variance t-test confidence interval (-2.0)- (-5.1) = 3.2 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1

14.2.8 Change in Use of Supplemental Oxygen at 1 Year

At the end of 1 year of follow-up, Zephyr EBV Subjects in the Completed-Cases analysis of supplemental oxygen use showed an increased use of 109.5 liters / day and the Control Subjects showed an increased use of 172.3 liters / day, a net Zephyr EBV treatment benefit of −62.8liters a day (95% CI −302.5, 176.9).

Table 93 Change in Use of Supplemental Oxygen at 1 Year (CC)

Supplemental O_2 – Change from Baseline	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
CC Subjects (liters / day)	172.3 (744.05) 72 0.0 (-1680.0, 3150.0)	109.5 (1100.61) 171 0.0 (-3840.0, 4965.0)	-62.8 (-302.5, 176.9)[1]

[1] Difference of means and unequal variance t-test confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25.1

14.3 Matched 3, 6, and 12 Month FEV_1 and 6MWT Data

A matched-groups data analysis was performed for FEV_1 and 6MWT for Completed Cases subjects with relevant data at baseline, three months, six months and one year to investigate the timing and durability of treatment response in comparable subjects. There were 133 Zephyr EBV Subjects and 57 Control Subjects with FEV_1 data at baseline, three months, six months, and one year. There were 129 Zephyr EBV Subjects and 56 Control Subjects with 6MWT data at baseline, three months, six months, and one year.

14.3.1 Matched 3, 6, and 12 Month FEV_1 Outcomes

Matched-group Zephyr EBV Subjects had a net increase in FEV_1 of 3.9% compared with the matched-groups Control Subjects at three months (95% CI, -0.7 – 8.5%). This improvement increased to a net increase in FEV_1 of 7.1% compared with the matched-pairs Control Subjects at six months (95% CI, 2.7 – 11.5%) and to 8.8% at one year (95% CI, 4.1 – 13.5%).

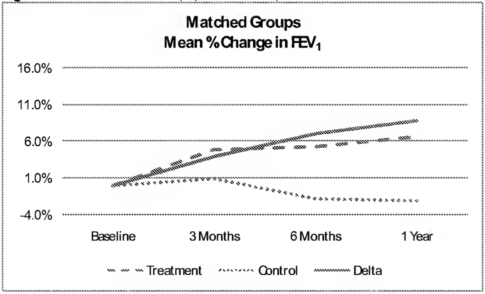
Table 94 Matched 3, 6, and 12 Month % Change in FEV_1

Percent Change in FEV_1	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
3 Months	0.9 (11.8) 57 -1.2 (-26.4, 39.2)	4.9 (19.8) 133 1.2 (-33.7, 88.3)	3.9 (-0.7, 8.5)
6 Months	-1.8 (11.3) 57 -3.4 (-27.7, 25.5)	5.3 (19.0) 133 3.8 (-38.3, 65.7)	7.1 (2.7, 11.5)
1 Year	-2.1 (11.0) 57 -2.0 (-29.1, 23.0)	6.7 (21.6) 133 2.0 (-33.9, 88.4)	8.8 (4.1, 13.5)

[1] Difference of means and unequal variance t-test confidence interval (4.9)- (0.9) = 3.9 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:9

This continued benefit on disease progression throughout 1 year of follow-up as measured by FEV_1 is demonstrated in the following chart.

Figure 24 Chart: Matched 3, 6, and 12 FEV_1 Outcomes



Source: Attachment 3, Amended Statistical Analysis Report, Table 25:9

14.3.2 High Heterogeneity Subgroup Matched 3, 6, and 12 Month FEV_1 Outcomes

Matched-group Zephyr EBV Subjects in the High Heterogeneity Subgroup had a net increase in FEV_1 of 7.6% compared with the matched-groups Control Subjects at three months (95% CI, 0.8 – 14.3%). This improvement increased to a net increase in FEV_1 of 11.9% compared with the matched-pairs Control Subjects at six months (95% CI, 4.9 – 18.5%) and to 13.7% at one year (95% CI, 6.6 – 20.8%).

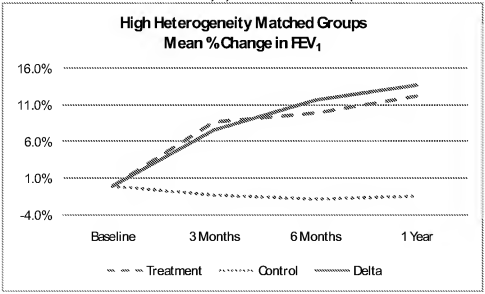
Table 95 High Heterogeneity Subgroup: Matched 3, 6, and 12 Month % Change in FEV_1

Percent Change in FEV_1	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta [1] (95% CI)
3 Months	0.9 (11.4) 30 -1.3 (-26.4, 32.7)	8.5 (21.9) 66 3.5 (-26.1, 88.3)	7.6 (0.8, 14.3)
6 Months	-1.8 (11.5) 30 -4.2 (-19.2, 25.5)	10.0 (22.0) 66 7.7 (-38.3, 65.7)	11.9 (5.1, 18.6)
1 Year	-1.4 (11.4) 30 0.7 (-29.1, 21.8)	12.3 (23.6) 66 9.6 (-32.5, 88.4)	13.7 (6.6, 20.8)

[1] Difference of the means and unequal variance t-test confidence interval (10.0)- (-1.8) = 11.9 due to rounding)
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:13

This continued benefit on disease progression in the High Heterogeneity Subgroup throughout 1 year of follow-up as measured by FEV_1 is demonstrated in the following chart.

Figure 25 Chart: High Heterogeneity Subgroup Matched 3, 6, and 12 Month FEV_1 Outcomes



Source: Attachment 3, Amended Statistical Analysis Report, Table 25:13

14.3.3 Matched 3, 6, and 12 Month 6MWT Outcomes

Matched-pairs Zephyr EBV Subjects had a net increase in 6MWT of 7.4% compared with the matched-pairs Control Subjects at three months (95% CI, 1.2 – 11.5%). At six months, Zephyr EBV Subjects had a net increase in 6MWT of 6.8% compared with the matched-pairs Control Subjects (95% CI, 0.5– 13.1%), and a net increase of 5.5% at 12 months (95% CI, -0.7 – 11.7%).

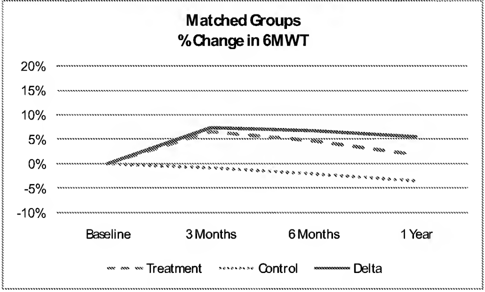
Table 96 Matched 3, 6, and 12 Month Data for Percent Change in 6MWT

Percent Change in 6MWT	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)
3 Months	0.3 (19.2) 56 -0.8 (-55.4, 50.0)	6.9 (18.3) 129 6.6 (-43.7, 83.2)	7.4 [2] (1.2, 11.5)[3]
6 Months	-1.2 (24.5) 56 -2.1 (-54.9, 71.4)	4.9 (22.3) 129 4.7 (-53.9, 108.0)	6.8 [2] (0.5, 13.1)[3]
1 Year	-3.5 (16.7) 56 -3.3 (-63.1, 31.6)	1.9 (24.8) 129 2.5 (-72.3, 108.0)	5.5 [1] (-0.7, 11.7)

[1] Difference of means and unequal variance t-test confidence interval (1.9 – (-3.5) = 5.5 due to rounding)
[2] Difference of medians
[3] Non-parametric confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:9

The chart below demonstrates that the 6MWT benefit in the Zephyr EBV Treatment group peaks early and then declines at a rate similar to that of the Control group. Thus, the separation at one year is approximately the same as at 3 and 6 months.

Figure 26 Chart: Matched 3, 6, and 12 Month 6MWT Outcomes



Source: Attachment 3, Amended Statistical Analysis Report, Table 25:9

14.3.4 High Heterogeneity Matched 3, 6, and 12 Month 6MWT Outcomes

Matched-pairs Zephyr EBV Subjects in the High Heterogeneity Subgroup had a net increase in 6MWT of 9.4% compared with the matched-pairs Control Subjects at three months (95% CI, 2.1 – 17.7%). At six months, High Heterogeneity Zephyr EBV Subjects had a net increase in 6MWT of 14.7% compared with the matched-pairs Control Subjects (95% CI, 7.6 – 25.2%), and a net increase of 11.0% at 12 months (95% CI, 1.0 – 21.0%).

Table 97 High Heterogeneity Subgroup: Matched 3, 6, and 12 Month Data for Percent Change in 6MWT

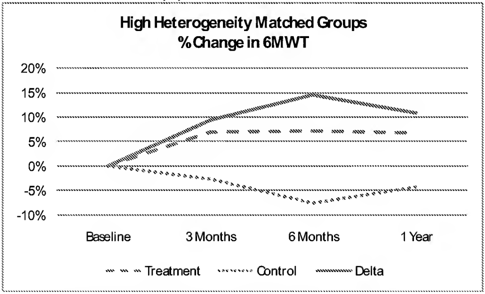
Percent Change in 6MWT	Control Mean (SD) N Median (Min, Max)	Zephyr EBV Mean (SD) N Median (Min, Max)	Delta (95% CI)
3 Months	-3.1 (20.9) 29 -2.6 (-55.4, 50.0)	7.8 (21.5) 65 6.9 (-43.7, 83.2)	9.4 [2] (2.1, 17.7) [3]
6 Months	-7.4 (23.3) 29 -7.5 (-54.9, 66.7)	9.2 (25.4) 65 7.1 (-53.8, 108.0)	14.7 [2] (7.6, 25.2) [3]
1 Year	-4.3 (18.8) 29 -3.4 (-63.1, 25.0)	6.7 (29.2) 65 6.3 (-72.3, 108.0)	11.0 [1] (1.0, 21.0)

[1] Difference of means and unequal variance t-test confidence interval
[2] Difference of medians (6.9) - (-2.6) = 9.4 and (7.1) - (-7.5) =14.7 due to rounding)
[3] Non-parametric confidence interval
Source: Attachment 3, Amended Statistical Analysis Report, Table 25:13

The chart below demonstrates that the 6MWT benefit in the High Heterogeneity Zephyr EBV Treatment group seems to peak at 6 months.

Thus, the separation at one year is approximately the same as at 3 months.

Figure 27 Chart: High Heterogeneity Subgroup Matched 3, 6, and 12 Month 6MWT Outcomes

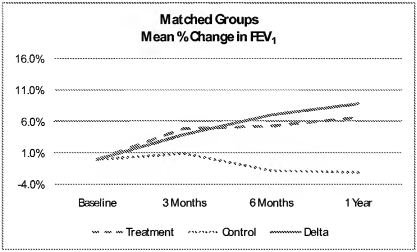


Source: Attachment 3, Amended Statistical Analysis Report, Table 25:13

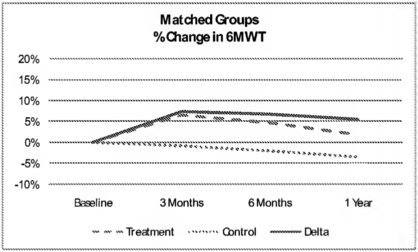
14.4 Summary: Effectiveness Outcome Measures at 1 Year

Although the VENT Pivotal Study was not designed or sized to test significance of effectiveness measures at 1 year of follow-up, outcome measurements continued to favor Zephyr EBV Treatment over the Control through this time point.

From matched grouped comparisons of results at 3 months, 6 months, and 1 year FEV1 appears to continue to improve in the Zephyr EBV Treatment Group through the entire 1 year follow-up. The treatment effect remained statistically-significant at 1 year.



Zephyr EBV Treatment Group benefit in 6MWT appears to peak at 3 months while retaining most of the net benefit through 1 year for those Subjects with matched data. However, the treatment effect was not statistically-significant at 1 year.



15.0 CONCLUSIONS

Overview: The VENT Pivotal Trial was a randomized, controlled, multi-center trial that enrolled subjects with severe heterogeneous emphysema to assess the safety and effectiveness of the Emphasys Endobronchial Valve (Zephyr EBV) and procedure compared to optimal medical management. Zephyr EBV Subjects underwent bronchoscopic Zephyr EBV implantation and both Zephyr EBV Subjects and Control Subjects received optimal medical management. Six month follow-up for all subjects included assessment of a variety of relevant pulmonary and general outcome measures as evaluated by specific spirometry, body plethysmography, diffusing capacity, QoL and exercise tests; a 12 month follow-up visit was also performed. The co-primary effectiveness outcomes were the percent change in both FEV_1 and 6MWT in Zephyr EBV Subjects compared to Control Subjects determined at the 6 month follow-up visit; superiority had to be demonstrated in both measures to meet the outcome. The primary safety outcome was the Major Complication Composite at 6 months.

Validity of Results: The VENT Pivotal Trial enrolled 321 subjects and randomization resulted in highly comparable treatment groups with severe, heterogeneous emphysema (101 Control Subjects, 220 Zephyr EBV Subjects). Study subjects were assessed, treated and followed under the provisions of the approved study protocol, with a high degree of subject, device and imaging accountability. Monitoring procedures, data handling and statistical practice ensured that the results reported in this Clinical Study Report are valid scientific evidence.

Procedure: The bronchoscopic initial implantation procedure was quick (33.8 minutes) with 71.5% of subjects treated with conscious sedation only. A mean of 3.8 valves were implanted per Zephyr EBV Subject, with Acute Technical Success in 94.9%. Valves were frequently removed and replaced without difficulty during implantation procedures, allowing the operator to achieve optimal positioning.

Primary Effectiveness Outcome: The VENT Pivotal Trial met its co-primary outcomes, with a significant percent improvement in both FEV_1 and 6MWT in Zephyr EBV Subjects when compared with Control Subjects at 6 months of follow-up. These significant differences existed whether the analysis was performed with multiple imputation for missing values or with completed cases only, and were confirmed by pre-specified multivariate analysis.

Intent-to-treat: 1° Effectiveness Outcomes	Delta	p value
Percent Change in FEV_1	6.8 (2.1, 11.5)	**0.002**
Percent Change in 6MWT	5.8 (0.5, 11.2)	**0.019**

Secondary Effectiveness Outcomes: The four secondary effectiveness outcomes were met, with the changes in the St. Georges Respiratory Questionnaire, the Modified Medical Research Council Dyspnea Scale, the maximum workload measured by cycle ergometry, and the use of supplemental oxygen all significantly better in the Zephyr EBV Subjects when compared with the Control Subjects.

Intent-to-treat: 2° Effectiveness Outcomes	Delta	p value
SGRQ (points)	–3.4 (–6.6, –0.3)	**0.0167**
mMRC (points)	–0.26 (–0.49, –0.02)	**0.0183**
Maximum workload (watts)	3.8 (0.2, 7.4)	**0.0203**
Supplemental O_2 (L / day)	–12.0 (–76.7, 52.7)	**0.0198**

Primary Safety Outcome: At 6 months of follow-up, Control Subjects had a 1.2% rate of Major Complication Composite events (MCCs) compared with 6.1% for Zephyr EBV Subjects, a trend that was not significant ($p = 0.0748$). This difference was primarily driven by a trend to greater 6 month mortality in the Zephyr EBV Subjects with 6 deaths: 3 from respiratory failure, one from cancer, one from ischemic colitis and 1 from massive hemoptysis, of which only the death from hemoptysis was related to the device.

All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the Control Subjects and 3.7% for the Zephyr EBV Subjects ($p = 0.8763$, log rank test). The MCC rate in the second 6 months of follow-up was almost identical: 4.6% for Control Subjects and 4.7% for Zephyr EBV Subjects. Zephyr EBV treatment was not significantly associated with the occurrence of MCCs through 6 months.

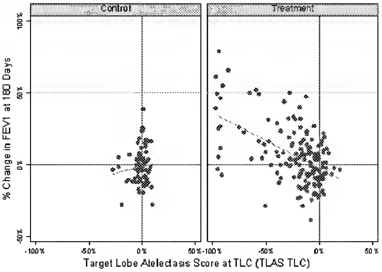
Additional Pre-Specified Analyses: The change in BODE Index was significantly better in the Zephyr EBV Subjects than Control Subjects (p.0.0024). Percent changes in residual volume and diffusing capacity were slightly but not significantly better in Zephyr EBV Subjects, and the Quality of Wellbeing instrument revealed no difference between the groups. Technical success (complete lobar exclusion) was found in 56.2% of Zephyr EBV Subjects on HRCT at 6 months. There was a trend towards higher hospitalization

rates for Zephyr EBV Subjects (27.1%) compared with Control Subjects (16.1%) through 6 months, which was borderline significant ($p = 0.0522$); this difference appeared to be driven largely by study-related valve removal procedures and diminished during the last 6 months of follow-up.

Clinical Importance of Zephyr EBV Treatment Response:

Responder analyses performed at generally accepted levels of minimal clinically important differences (MCIDs) on key outcome measures revealed that single lobe Zephyr EBV treatment confers a consistent pattern of clinical benefit for FEV_1, 6MWT, SGRQ, mMRC, maximum workload by cycle ergometry and the BODE Index, all key clinical indicators of disease status.

Treatment, Volume Reduction and FEV_1: Analyses of relevant study variables supported the primary rationale of Zephyr EBV treatment, which was that Zephyr EBV treatment led to reduction in target lobe volume reduction (TLVR), which in turn led to improvement in changes in pulmonary function at 6 months.



The VENT Pivotal Trial prospectively assessed the hypothesized mechanism of treatment effect, which was to cause volume loss in non-ventilating lung with resulting improved ventilation in healthier lung parenchyma. Study results strongly suggest this to be the case. Unilateral treatment of subjects with heterogeneous emphysema with Zephyr EBVs elicited substantial target lobe volume reduction (TLVR) as measured by target lobe atelectasis score ($TLAS_{TLC}$). Zephyr EBV Subjects showed a 20.6% reduction in lobar volume compared with 1.7% loss in Control Subjects.

Furthermore, the TLVR resulting from Zephyr EBV treatment was highly associated with improved FEV_1 in Zephyr EBV Subjects at 6 months of follow-up ($r^2 = 0.2785$, $p = 0.0000$).

Relevant clinical factors that would be associated with a closed system (exclusion of all lobar bronchi with Zephyr EBV devices and completeness of interlobar fissures to prevent collateral air flow) were highly associated with the degree of TLVR as measured by $TLAS_{TLC}$. Zephyr EBV Subjects with Technical Success (complete lobar exclusion) had a mean $TLAS_{TLC}$ of −28.1% compared with −11.1% for Zephyr EBV Subjects without Technical Success. Zephyr EBV Subjects with complete interlobar fissures had mean $TLAS_{TLC}$ of −40.1% (left lung) and −33.0% (right lung) compared with −20.7% and −4.4% respectively for incomplete fissures. The combination of Technical Success and Complete Fissure Integrity resulted in a mean $TLAS_{TLC}$ of −54.8% compared with −6.4% when both factors were absent.

Safety Profile: A review of the adverse event (AE) profile of the Zephyr EBV reveals that implanted subjects had higher rates of emphysema related conditions, including such manifestations as COPD exacerbations, other pulmonary infections, increase shortness of breath and hypoxemia. Use of the Zephyr EBV was associated with higher rates of hemoptysis and atypical chest pain. When considering serious adverse events (SAEs) only COPD exacerbations requiring hospitalization and hemoptysis emerged as significantly more frequent events. For both AEs and SAEs, event rates in the Zephyr EBV Subjects tended to decline during study follow-up and approach the rates of the Control Subjects. These declines in adverse event rates appeared to be independent of valve removals.

Key aspects of the Zephyr EBV safety profile that have emerged from the VENT Pivotal Trial include the following characteristics:

- Use of the Zephyr EBV was associated with increased rates of COPD related adverse events, hemoptysis, atypical chest pain and perhaps rehospitalization through 1 year of follow-up.
- Granulation tissue, valve migration, and pneumonia distal to the valve are adverse events that are specifically related to the use of this device.
- These phenomena diminish with time.
- The device can be safely removed with a high degree of success, and when valve removal is performed as a result of an adverse event, the adverse event generally resolves.
- There was no difference in all-cause mortality between the Control Subjects and Zephyr EBV Subjects over the 1-year study follow-up.

Outcome Measures at One Year: Although the VENT Pivotal Study was not designed or sized to test significance of effectiveness measures at 1 year of follow-up, outcome measurements continued to favor Zephyr EBV Treatment over the Control through this time point. These results were confirmed by responder analysis and matched-pairs analysis.

Conclusion: The VENT Pivotal Trial results demonstrate that unilateral treatment of severe heterogeneous emphysema in medically optimized subjects achieved substantial additional improvement in a variety of outcomes including FEV_1 and 6MWT over that achieved by approved medical treatments alone. This level of additional improvement in maximally treated, severely ill subjects is clinically important. Such findings constitute valid scientific evidence demonstrating the effectiveness of the Zephyr EBV device in improving important subjective and objective measures of health in a population of subjects with severe heterogeneous emphysema. While there are several clear risks of the use of the Zephyr EBV device, these are generally minor, tend to diminish over time, and usually resolve after device removal. Use of the Zephyr EBV in patients with severe heterogeneous emphysema provides an important palliative benefit that exceeds the attendant risks.

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17.0 CHANGE TRACKER

Note: Section, Table and other numbering is for the version contained in that column.

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Terminology throughout	"endpoint"	"outcome" and "outcome measure"	To clarify the difference between study measures and specifically defined primary and secondary outcomes for those measures
Terminology throughout	"Emphysema Score"	"Density Score"	The terms are synonymous, Density Score is the currently preferred usage
Convention throughout	Mean differences reported universally	Median differences reported for non-parametric distributions with equal variances. Mean difference reported when a parametric inference test is or would be used.	Medians are a more appropriate estimate of the differences between distributions when the distribution is non-parametric.
Synopsis	Revised to reflect changes in Clinical Study Report overall		Revised to reflect changes in body of document
Section 1.0	No changes		No changes
Section 2.0	Section 2.1, Study Responsibilities	Section 2.1, Study Responsibilities	Reduced roles of consultants. Minor changes clarifying responsibilities
Section 3.0	Section 3.2 Zephyr Delivery Catheter and Zephyr Loader System	Section 3.2 Zephyr Delivery Catheter and Zephyr Loader System	Added footnote to delivery catheter photo (figure 3) to clarify change made post enrollment

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Section 4.5, SAP	Section 4.5.2 Error and Bias Control Section 4.5.3: Analytic Methods .	Section 4.5.2 Error and Bias Control Section 4.5.3: Analytic Methods	Removed "maximally blinded" qualifier for CEC due to ambiguity of term Language regarding populations and windows for analysis was edited for clarity Modified "intent-to-treat (ITT)" to "multiple-imputation intent-to-treat (ITT)" Added "results combined for analysis"
Section 4.5, SAP	Section 4.5.5, Safety Endpoints Section 4.5.6, Effectiveness Endpoints Section 4.5.7, Additional Analyses	Section 4.5.5, Safety Measures and Outcomes Section 4.5.6, Effectiveness Measures and Outcomes	Composite of Death/LVRS/transplant as an outcome measure not included in revised CSR (but still in Statistical Analysis Report (SAR)) To clarify which outcomes measures were pre-specified and which were *post hoc* To add and justify certain analyses performed in response to FDA queries: • *Post hoc* responder analyses • *Post hoc* analyses of treatment, target lobe volume reduction and FEV_1 response • *Post hoc* 1 year effectiveness outcome measures
Section 4.6, Imaging Procedures	Section 4.6 Imaging Procedures Section 4.6.3, Quantitative Image Analysis	Section 4.6 Imaging Procedures Section 4.6.3, Quantitative Image Analysis	More specificity added to role of core lab Revised for clarity
Section 4.6, Imaging Procedures	[none]	Section 4.6.4, Density (Emphysema) and Heterogeneity Scoring	Added to clarify procedures

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Section 4.6, Imaging Procedures	Section 4.6.4 Fissure Integrity Assessment	Section 4.6.5 Fissure Integrity Assessment	Added clarification and image.
Section 4.6, Imaging Procedures	[none]	Section 4.6.7, Target Lobe Atelectasis Score (TLAS) Methodology	Added to clarify procedures
Section 4.7, Changes in the Conduct of the Study	[none]	Section 4.7.3, Additional Analyses Resulting from FDA Communications	Added to clarify additional analyses
4.8, Protocol Deviations	4.8, Protocol Deviations	4.8 Protocol Deviations	Minor corrections in text treatment of Table 4, no change in Table 4.
4.9, Study Definitions	4.9, Study Definitions	4.9, Study Definitions	Corrections and additions to definitions for clarity and completeness
Section 5.0, Study Accountability and Population	Section 5.5, Distribution of Subjects by Study Site and Strata including Table	Section 5.1 includes statement that stratification was successful and refers reader to SAR for details	Section 5.5 and Table deleted as unnecessary for Clinical Study Report (all data still in SAR)
Section 6.0 Baseline Subject Characteristics	[none]	Section 6.7, BODE Indices Section 6.8, SGRQ Scores Section 6.9, mMRC Dyspnea Scale Scores Section 6.12 HRCT Characteristics	Correct an inadvertent omission by including important baseline data regarding secondary effectiveness outcome measures Correct an inadvertent omission and provide more clarity regarding heterogeneity in response to FDAs deficiency questions
Section 7.0	Minor changes		Minor changes

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Primary Effectiveness Outcome	Section 8.1, Primary Effectiveness Endpoint 8.1.1 – Mean Percent Changes in FEV1 and 6MWT- Univariate Tests Table 33 Primary Effectiveness Endpoint… 8.1.2 – Multivariate 8.1.3.1 – Completed Cases	Section 8.2, Primary Effectiveness Outcomes 8.2.1 – Percent Change in FEV1 and 6MWT – Multiple Imputation Table 38 Primary Effectiveness Outcome… [none] 8.2.2 – Completed Cases	Reorganized for clarity. Removed multivariate ITT as a component of the Primary Effectiveness Outcome per FDA statistician. Removed table 32 for same reason. Modified and updated per direction from FDA statistician. ITT multivariate no longer done per FDA statistician.
Secondary Effectiveness Outcomes	Section 8.2, Secondary Effectiveness Endpoints 8.2.1 – SGRQ 8.2.2 – mMRC 8.2.3 – Maximum workload 8.2.4 – Supplemental oxygen	Section 8.3, Secondary Effectiveness Outcomes 8.3.1 – SGRQ 8.3.2 – mMRC 8.3.3 – Maximum workload 8.3.4 – Supplemental oxygen	Reorganized for clarity. Change from ITT to multiple imputation
Primary Safety Outcome	Section 9.2, Primary Safety Endpoint: Major Complications Composite	Section 9.2, Primary Safety Outcome: Major Complications Composite	Reorganized for clarity. No change in data or conclusions presented
Primary Safety Outcome – Related Analyses	Section 9.3.1, All-Cause Mortality Section 9.2.1, Cox Regression Analysis of MCCs Section 9.2.2, MCC by Time Period Section 9.4.8, MCC Rates by Calendar Quarter of Follow-up	Section 9.3.1, All-Cause Mortality Section 9.3.2, Cox Regression Analysis of MCCs Section 9.3.3, MCC by Time Period Section 9.3.4, MCCs by Valve Removal Status through One Year	Reorganized for clarity. No change in data or conclusions presented Brief cause of death added to Table 45, Summary: Subjects with One or More MCCs

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Additional Pre-Specified Analyses	Section 10.2.3, Mean % Change in RV Section 10.2.4, Mean % Change in Diffusing Capacity Section 10.2.2, Mean Change in QWB Section 10.2.1, Mean Change in BODE Index Section 10.3, Technical Success Section 9.3.1, Rehospitalization	Section 10.2.1, Mean % Changes in RV Section 10.2.2, Mean % Changes in Diffusing Capacity Section 10.2.3, Mean Change in QWB Section 10.2.4, Mean Change in BODE Index Section 10.2.5, Technical Success Section 10.2.6, Rehospitalization	Reorganized for clarity. No change in data or conclusions presented
Pre-Specified Subgroup Analyses	Section 10.4, FEV_1 and 6MWT: Effect of Lobar Exclusion Section 8.1.3.2, Subgroup Analysis: Heterogeneity Score ≥ 15%	Section 10.3.1, Technical Success, FEV_1 and 6MWT Outcomes Section 10.3.2, Heterogeneity Score ≥ 15%, FEV_1 and 6MWT Outcomes	Reorganized for clarity. No change in data or conclusions presented
Pre-Specified Subgroup Analyses	[none]	Section 10.3.3, Complete Fissure Integrity and FEV_1	Correct an inadvertent omission by including this important pre-specified subgroup analysis
Responder Analyses – Pre-Specified	8.1.3.3, ≥ 15% Improvement in FEV_1 8.1.3.4, ≥ 15% Improvement in 6MWT	11.2.3, ≥ 15% Improvement in FEV_1 11.3.3, ≥ 15% Improvement in 6MWT	Reorganized for clarity. No change in data or conclusions presented
Responder Analyses – Pre-Specified	[none]	11.2.1, Maintained (≥ 0% improvement) in FEV_1 11.3.1, Maintained (≥ 0% improvement) in 6MWT	Correct an inadvertent omission by including these important pre-specified responder analyses

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Responder Analyses – From Analysis Plan	[none]	All By High Heterogeneity Subgroup: 11.2.2 Maintained (≥ 0% improvement) in FEV_1 11.2.4 Maintained (≥ 0% improvement) in 6MWT 11.3.2 ≥ 15% Improvement in FEV_1 11.3.4, ≥ 15% Improvement in 6MWT	Analyses performed in response to FDA query regarding clinical importance of demonstrated statistical effects
Responder Analyses – *Post hoc*	[none]	11.4.1, ≥ 4 and ≥ 8 Point Improvement in SGRQ 11.4.2, ≥ 1 Point Improvement in mMRC 11.4.3, ≥ 10 Watt Improvement in Maximum Workload during Cycle Ergometry 11.4.4, ≥ 1 Point Improvement in BODE Index	Analyses performed in response to FDA query regarding clinical importance of demonstrated statistical effects

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Post hoc investigation of mechanism of treatment effect	10.6.1, Zephyr EBV Treatment Leads to TLVR 10.5.2, Effect of TLVR on FEV_1 and 6MWT 10.6.5, Complete Lobar Exclusion (Technical Success) and $TLAS_{TLC}$ 10.6.4, Fissure Completeness and $TLAS_{TLC}$ 10.6.6, EBV Subjects with Complete Lobar Exclusion (Technical Success) and Complete Fissures by Target Lung	12.2.1, Zephyr EBV Treatment Leads to TLVR 12.2.2, TLVR is Significantly Associated with Improved FEV_1 at 6 Months 12.3.1, Technical Success and TLVR 12.3.2, Fissure Integrity and TLVR 12.3.3, Technical Success, Fissure Integrity and TLVR 12.4.1, Technical Success, Fissure Integrity and FEV_1	Reorganized for clarity. No change in data or conclusions presented except: • 6MWT results not included in revised CSR (but still in SAR) • Left and right lung sub-analyses in March 18 CSR Section 10.6.6 not included in revised CSR (but still in SAR)
Safety Profile	9.4.1, Adverse Events 9.4.9, Adverse Events with Higher Rates in Zephyr EBV Subjects by Quarter of F/U 9.4.10, Serious Adverse Events 9.4.11, Serious Adverse Events by Calendar Quarter of F/U through 1 Year 9.4.12, Device-Related Adverse Events 9.4.12, Procedure-Related Adverse Events	13.2.1, Adverse Events 13.2.2, Adverse Events by Quarter 13.2.3, Serious Adverse Events 13.2.4, Serious Adverse Events by Quarter 13.2.5, Device-Related Adverse Events 13.2.6, Procedure-Related Adverse Events	Reorganized for clarity. No change in data or conclusions presented except: • Tables listing device- and procedure-related adverse events not included in revised CSR (but still in SAR)
Safety Profile	9.4.2, Granulation Tissue 9.4.3, Valve Expectoration or Migration 9.4.4, Pneumonia Distal to Valves 9.4.7, Massive Hemoptysis 9.4.6, Valve Tx for Persistent Air Leak 9.4.5, Valve Removal During Study F/U	13.3.1, Granulation Tissue 13.3.2, Valve Expectoration or Migration 13.3.3, Pneumonia Distal to Valves 13.3.4, Massive Hemoptysis 13.3.5, Valve Tx for Persistent Air Leak 13.4, Valve Removal During Study F/U	Reorganized for clarity. Addition of footnote to 13.3.2 to clarify potential root causes of valve migrations No change in data or conclusions presented

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Post hoc Outcome Measures at One Year	8.3.1, Mean % Changes in FEV_1 at 1 Year 8.3.2, Mean % Changes in 6MWT at 1 Yr. 8.3.3, Mean Changes in SGRQ at 1 Year 8.3.4, Mean Changes in mMRC at 1 Year 8.3.5, Mean Changes in Maximum Workload at 1 Year 8.3.6, Mean Changes in Supplemental Oxygen at 1 Year	14.2.1, Percent Change in FEV_1 at 1 Year 14.2.2, High Heterogeneity Percent Change in FEV_1 at 1 Year 14.2.3, Percent Change in 6MWT at 1 Yr. 14.2.4, High Heterogeneity Percent Change in FEV_1 at 1 Year 14.2.3, Change in SGRQ at 1 Year 14.2.4, Change in mMRC at 1 Year 14.2.5, Change in Maximum Workload at 1 Year 14.2.6, Changes in Supplemental Oxygen at 1 Year	Reorganized for clarity. Analyses performed in response to FDA query regarding durability of treatment effect at one year
Post hoc Outcome Measures at One Year	[none]	14.3 Matched 3, 6, and 12 Month FEV_1 and 6MWT Data 14.3.1, Matched 3, 6, and 12 Month FEV_1 Outcomes 14.3.2, High Heterogeneity Subgroup Matched 3, 6, and 12 Month FEV_1 Outcomes 14.3.3, Matched 3, 6, and 12 Month 6MWT Outcomes 14.3.4, High Heterogeneity Subgroup Matched 3, 6, and 12 Month 6MWT Outcomes	Additional analyses performed in response to FDA query regarding durability of treatment effect at one year

Reference	CSR Version dated March 18, 2008	CSR Version dated August 8, 2008	Rationale
Conclusions	11.0, Discussion and Conclusions	15.0, Conclusions	Revised to reflect changes in body of document
References	12.0, References	16.0, References	Additional references regarding responder analyses and MCIDs included